New onset heart failure

Brouwers, Franciscus Paulus Johannes

New onset heart failure:
Origin and manifestation

Franciscus P. J. Brouwers

Brouwers F.P.J.
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Origin and manifestation

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Promotores:
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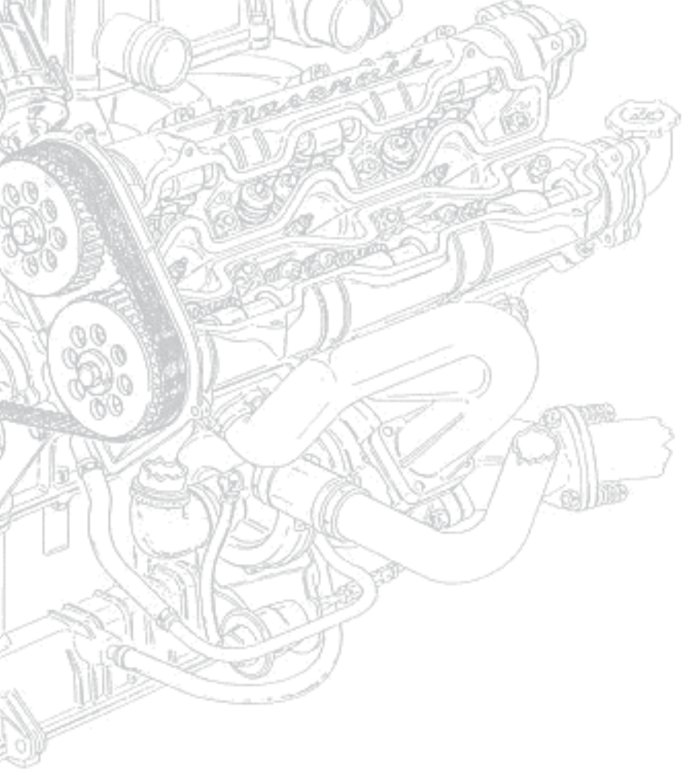
Table of Contents



Introduction

Heart failure - origin

Heart failure is the term used to describe an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissue.[1] Clinically, heart failure is a syndrome in which patients have typical symptoms (e.g. breathlessness and fatigue) and signs (e.g. oedema, rales, elevated jugular venous pressure) caused by abnormal cardiac structure or function.[1] It is a progressive disorder that develops after a cardiovascular event either damages the heart muscle, resulting in loss of functioning cardiac myocytes, or disrupts the contractility of the myocardium.[2] This event may be acute (e.g. myocardial infarction); it may have a gradual onset (e.g. hemodynamic pressure of volume overloading); or it may have a hereditary cause (e.g. genetic cardiomyopathies).[2] Regardless of its nature, what all of these events have in common is that they result in a decline in the heart's pumping capacity. The subsequent decrease in cardiac output eventually activates a series of compensatory mechanisms intended to maintain cardiovascular homeostasis. The patient's cardiac function is thus preserved or only minimally depressed.[2] Past studies have shown us that the combination of compensatory mechanisms include early activation of the adrenergic nervous system and a salt and water-retaining system in order to preserve cardiac output.[3-5] Additionally, multiple vasodilatory molecules are released, including natriuretic peptides, nitric oxide and prostaglandins, to counteract the excessive vasoconstriction resulting from activation of aforementioned adrenergic and renin-angiotensin systems.[2, 6, 7] Therefore, patients with depressed cardiac function can remain asymptomatic or minimally symptomatic for years. However, a critical 'point of no return' is reached when patients become overtly symptomatic, with a resultant striking increase in morbidity and mortality. This progression to symptomatic heart failure is characterized by further activation of adverse pathways, involving neuro hormones and cytokines, as well as several adaptive changes within the myocardium.[2, 8] This process is referred to as left ventricular remodeling. In this phase, the patient resides in a stateof chronic activation of compensatory mechanisms for heart failure, which include structural alterations in the heart muscle, such as concentric left ventricular hypertrophy (following long-standing hypertension and aortic stenosis) or eccentric left ventricular hypertrophy (following chronic mitral or aortic regurgitation). Another type of compensatory left ventricular remodeling occurs in patients who have suffered myocardial infarction, in whom disproportionate dilatation of the left ventricle (i.e. infarct area) occurs, resulting in decreased systolic function.[1, 2]

Heart failure - manifestation

Approximately 2% of the adult population in developed countries has heart failure, although it mainly afflicts the elderly, affecting 6-10% of people over the age of 65 years.[9] The prevalence of heart failure in the United States is expected to increase to 20% of the population by 2040 (Figure 1). Heart failure is currently the single most common cause of hospitalization in persons 65 years of age or older, resulting in enormous costs to society and representing a major public health problem.[10] The prognosis of heart failure has improved over time, although it remains poor. Before 1990, the majority of patients died within five years of diagnosis and admission to hospital with progression of heart failure was frequent and recurrent, leading to an epidemic of heart failure hospitalization in many countries.[11-13] Effective treatment has improved outcome, with a relative reduction in hospitalizations of up to 30-50% in recent years, and a smaller but still significant decrease in mortality. Nevertheless, once acute heart failure ensues, 30% of patients die within one year, and the mortality rate after hospitalization exceeds that of most cancers.[12, 13]

The terminology used to describe heart failure is largely historical and based on measurement of left ventricular ejection fraction (LVEF). Mathematically, LVEF is the stroke volume (the end-diastolic volume minus the end-systolic

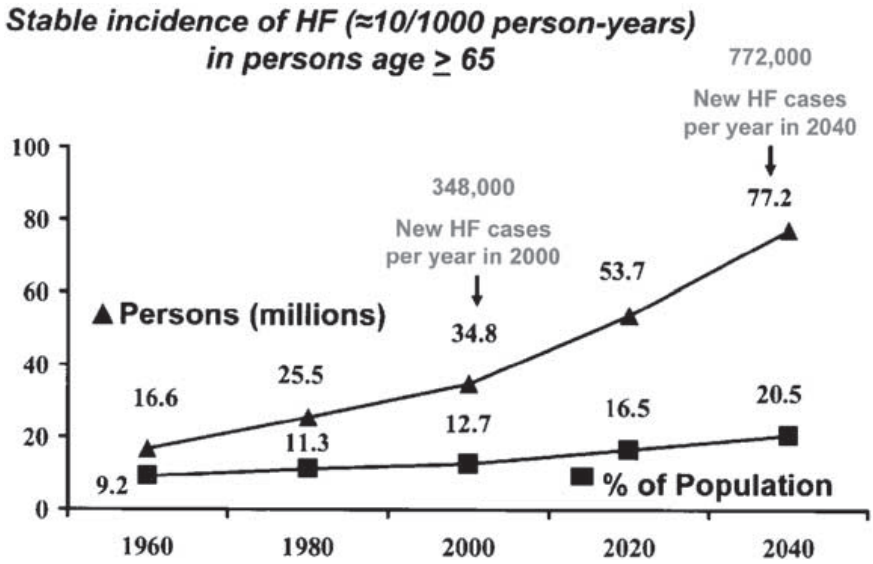


Figure 1 The expected prevalence of heart failure in the United States. Reprinted from Owan TE et al., Epidemiology of Diastolic Heart Failure, 47(5), 320-32, Copyright (2005), with permission from Elsevier

volume) divided by the end-diastolic volume. In patients with reduced contraction and emptying of the left ventricle, stroke volume is maintained through an increase in end-diastolic volume, because of left ventricular dilatation. In other words, the heart ejects a smaller fraction of a larger volume. The more severe the systolic dysfunction, the more the LVEF is reduced from normal and, generally, the larger the end-diastolic and end-systolic volumes.[1]

The LVEF is considered important in heart failure, and two syndromes are currently acknowledged: heart failure with reduced LVEF (HFrEF) and heart failure with preserved LVEF (HFpEF), see Table 1. In the past, HFrEF was referred to as 'systolic' heart failure, as opposed to 'diastolic' heart failure, which corresponded with HFpEF. Because diastolic dysfunction was observed in both HFrEF and HFpEF, the terms diastolic and systolic heart failure were discarded.[14, 15] It has been speculated that HFrEF and HFpEF either represent distinct forms of heart failure, or exist as part of one heart failure spectrum.[16] Recent structural, functional and molecular biological arguments support the theory that they are two discrete disease processes.[17-20]

In addition to differences in terminology, HFrEF and HFpEF differ with regard to pathophysiology, clinical characteristics and treatment.[16, 21, 22] HFrEF is far better understood in terms of pathophysiology and treatment. Coronary artery disease

Table 1 Diagnosis of heart failure

The diagnosis of HFrEF requires three conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF
3. Reduced LVEF
The diagnosis of HFpEF requires four conditions to be satisfied:
1. Symptoms typical of HF
2. Signs typical of HF
3. Preserved LVEF
4. Relevant structural heart disease (LV hypertrophy / LA enlargement) and / or diastolic dysfunction

HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction.

is responsible for approximately 60% HFrEF cases.[1, 23, 24] Other contributing factors include hypertension, alcohol abuse, chemotherapy, or 'idiopathic' dilated cardiomyopathy.[9, 25] Patients with HFpEF, on the other hand, are more likely to have hypertension, diabetes mellitus and atrial fibrillation. These patients are also older and more often female than those with HFrEF.[22] In the past two decades, many clinical trials successfully reduced mortality and morbidity rates in patients with HFrEF. Three neurohumoral antagonists – angiotensin converting enzyme inhibitors (or angiotensin receptor blockers), beta-blockers, and mineralocorticoid receptor antagonists – have been shown to substantially modify the course of HFrEF and reduce mortality, and should at least be considered in every patient.[1] Diuretics are commonly used to relieve the symptoms and signs of congestion. In contrast, no treatment to date has convincingly been shown to reduce mortality or morbidity in patients with HFpEF. Treatment of underlying co-morbidities, such as hypertension or atrial fibrillation, is considered important, but remains empirical. The use of diuretics to relieve signs and symptoms is similar to HFrEF.

The epidemiology of new onset HFrEF and new onset HFpEF is shifting. The incidence and prevalence of heart failure seems to have changed over the past decades, and the first signs of a decline in incidence of heart failure were reported in the past 10 years.[10, 26, 27] This decline may apply to HFrEF in particular, while the opposite may be true for HFpEF.[22, 28] There are several possible explanations for this development; this decrease in the incidence of HFrEF may be due to the fact that while large myocardial infarctions are the primary cause of HFrEF, such patients are now treated with primary angioplasty, leading to smaller infarction sizes, and thus fewer patients with HFrEF. Another explanation is that the diagnosis of HFpEF remains a particular challenge. Underrecognition of heart failure is more common in patients with HFpEF than in those with HFrEF, as LVEF remains a key factor for many physicians. In many cases, the diagnosis of heart failure is not considered when the LVEF is normal. In other words, the diagnosis of HFpEF is more difficult than the diagnosis of HFrEF, because it is largely one of exclusion, whereas potential non-cardiac causes for the patient's symptoms (such as anemia or chronic lung disease) must first be discounted.[1, 29] Finally, it has been suggested that a large proportion of patients with new onset HFpEF is mainly seen in the outpatient setting or by the general practitioner, and is therefore not included in hospital registries or clinical trials.[30]

In short, the incidence and prevalence of HFpEF is rising, both in absolute terms and relative to HFrEF, and there are currently no evidence-based treatment

options available. Additionally, there is increasing evidence that HFrEF and HFpEF follow different pathophysiologic pathways. Most data on HFrEF and HFpEF is derived from populations with prevalent heart failure, which leaves many unresolved issues regarding the development of both syndromes. Consequently, there is a need for prospective studies on the development of heart failure that distinguish between HFrEF and HFpEF. At the start of this thesis, in December 2009, several prospective studies on the development of heart failure in healthy subjects already existed,[31-33] however none distinguished between new onset HFrEF and HFpEF, due to lack of LVEF data. The PREVEND study offered an unique opportunity to study the natural development of both syndromes.

Study population

Data for this thesis were derived from the Prevention of REnal and Vascular ENdstage Disease (PREVEND) cohort, see Figure 2. The PREVEND study is a prospective, observational cohort study, aimed at assessing the impact of elevated urinary albumin loss in non-diabetic subjects on future cardiovascular and renal disease.[34] From 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (N = 85,421) were asked to send in a first morning urine sample and complete a short questionnaire on demographics and cardiovascular disease history, and 40,856 subjects responded (47.8%). All subjects with urinary albumin excretion (UAE) ≥10 mg/l (N = 7,786) in their morning urine as well as a randomly selected control group with a UAE <10 mg/l (N = 3,395) were invited to an outpatient clinic for a detailed assessment of cardiovascular and renal risk factors, including filling out questionnaires, anthropometrics, and blood and urine sampling. After excluding subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects unable or unwilling to participate, a total of 8,592 subjects completed the screening programme and underwent follow-up for an average of 12.5 years. This community-based population from the city of Groningen is characterised by a low prevalence of cardiovascular risk factors at baseline, long follow-up and standardized measurements of multiple clinical and biochemical parameters.

The Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) is an investigator-initiated, single-center, double-blind, randomized, placebo-controlled trial with a 2x2 factorial design.[35] Subjects were randomized to fosinopril 20 mg or matching placebo and to pravastatin 40 mg or matching placebo. The PREVEND IT is a predefined sub-study of the PREVEND program. The key entry criteria of the PREVEND IT were persistent

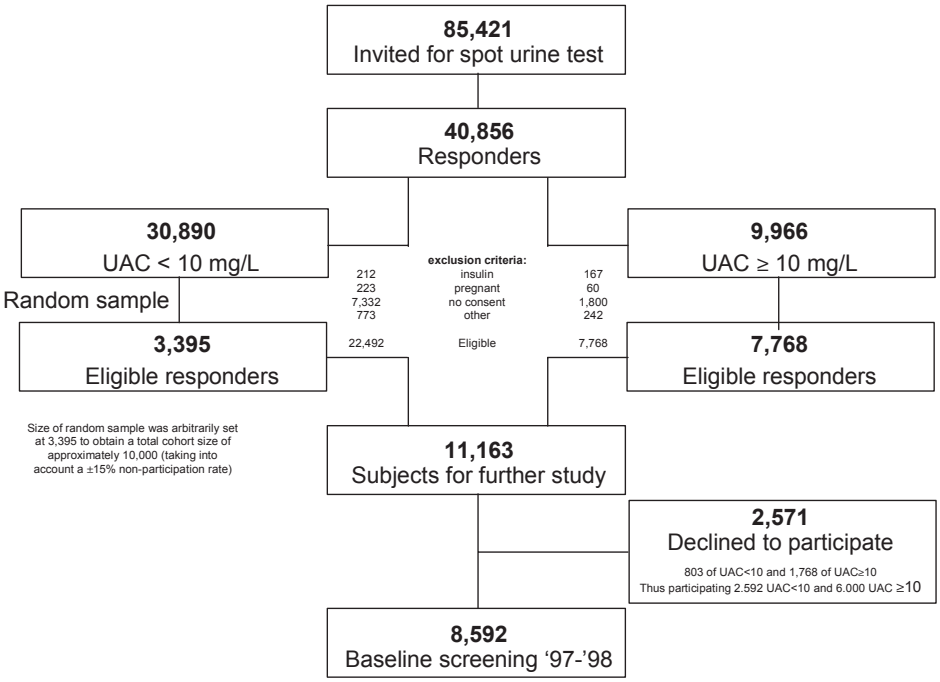


Figure 2 Design of the Prevention of Renal and Vascular Endstage Disease (PREVEND) cohort

microalbuminuria (one urinary albumin concentration ≥10 mg/l in an early morning spot urine and at least one 15 to 300 mg/24h in 2x24h urine samples), a blood pressure of <160/100 mmHg and no antihypertensive medication, a total cholesterol <8.0 mmol/l, or <5.0 mmol/l in case of previous myocardial infarction, and no lipid-lowering medication. From April 1998 to June 1999, 864 subjects were willing to participate in the PREVEND IT and were randomized to study medication.

Objectives and thesis outline

Data on the incidence of new onset HFrEF and HFpEF and its distinct risk factors in community-based cohorts are scarce, and studies directly comparing new onset HFrEF vs. HFpEF are lacking. This thesis aims to elucidate the epidemiology, population characteristics and biochemical data for new onset heart failure in subjects from a community-based cohort. We will differentiate between new onset HFrEF and new onset HFpEF, based on LVEF at time of diagnosis. The primary objective is to describe epidemiology of new onset heart failure, clinical characteristics and biomakers of new onset HFrEF and HFpEF, which is discussed in the first part of this thesis. In the second part, we support the aforementioned results with several secondary analyses, by associating the prognostic value of single biomarkers with poor cardiovascular outcome.

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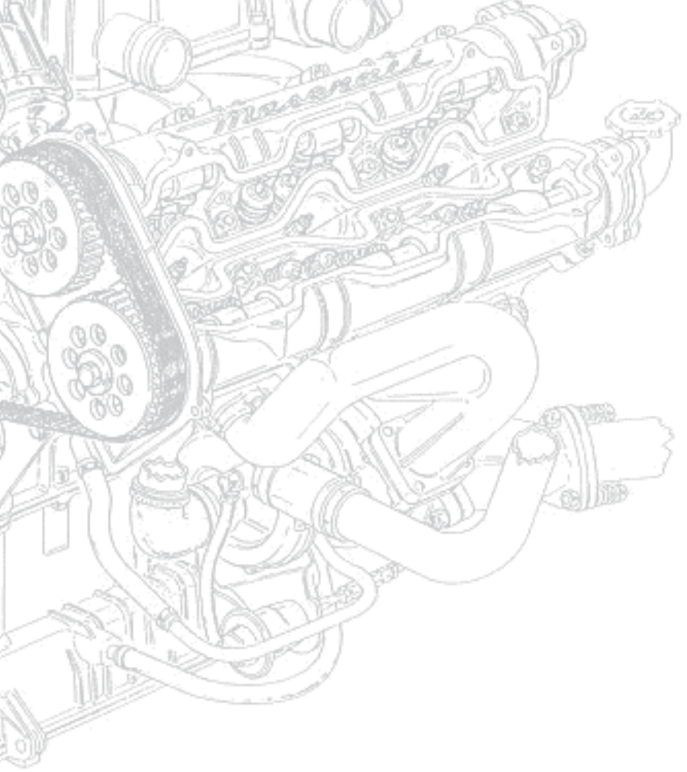
Part I
New onset heart failure



Chapter 1

The changing face of heart failure: are we really making progress?

Frank P. Brouwers
Wiek H. van Gilst
Dirk J. van Veldhuisen

European Journal of Heart Failure 2013;15(9):960-2

This editorial refers to 'The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden', by R. Zarrinkoub et al., doi: 10.1093/eurjhf/hft064

Approximately 1–2% of the adult population in developed countries has heart failure (HF), with the prevalence rising to ≥10% among persons 70 years of age or older.[1] HF is the single most frequent cause of hospitalization in persons 65 years of age or older and its societal costs are enormous, thereby presenting a large public health problem.[2] As the lives of patients with HF are prolonged by modern therapy, the prevalence of HF would be expected to increase, while morbidity and mortality rates remain high.[1] Indeed, the incidence and prevalence of HF seems to have changed over the past decades, and in the last 10 years the first signs of a decline in incidence of HF were reported.[2, 3]Interestingly, this decline may be particularly true for HF patients with reduced ejection fraction (HFrEF), while the opposite may be true for HF patients with preserved ejection fraction (HFpEF).[4, 5] This decrease in the incidence of HFrEF may be due to the fact that while large myocardial infarctions are the primary cause of HFrEF, such patients are nowadays quickly treated by primary angioplasty, leading to smaller infarction sizes, and fewer patients with HFrEF.[6]

In this issue of the journal, Zarrinkoub and colleagues are presenting new data on prevalence, incidence, mortality and survival of congestive HF in Sweden.[7] Using high quality health registries with almost complete recording, the authors were able to identify inhabitants of Stockholm with prevalent and incident HF, as well as detailed registration of the date of death of any cause, for a period of five consecutive years. After adjustment for demographic composition, the results were also extrapolated to the entire Swedish population.

In their study, the estimated prevalence of HF in Sweden was 2.2%. In absolute numbers and for every age category, more men were diagnosed with HF, except for subjects exceding 100 years of age. The incidence of HF in 2010 was 3.7/1000 person years in women and 3.9/1000 person years in men. From 2006 to 2010, the prevalence of HF remained the same for men, whereas women showed a modest decrease. Remarkably, the incidence of HF decreased relatively by 24% during this follow-up period, and no difference was observed between men and women. There was a similar decrease in mortality by 19%

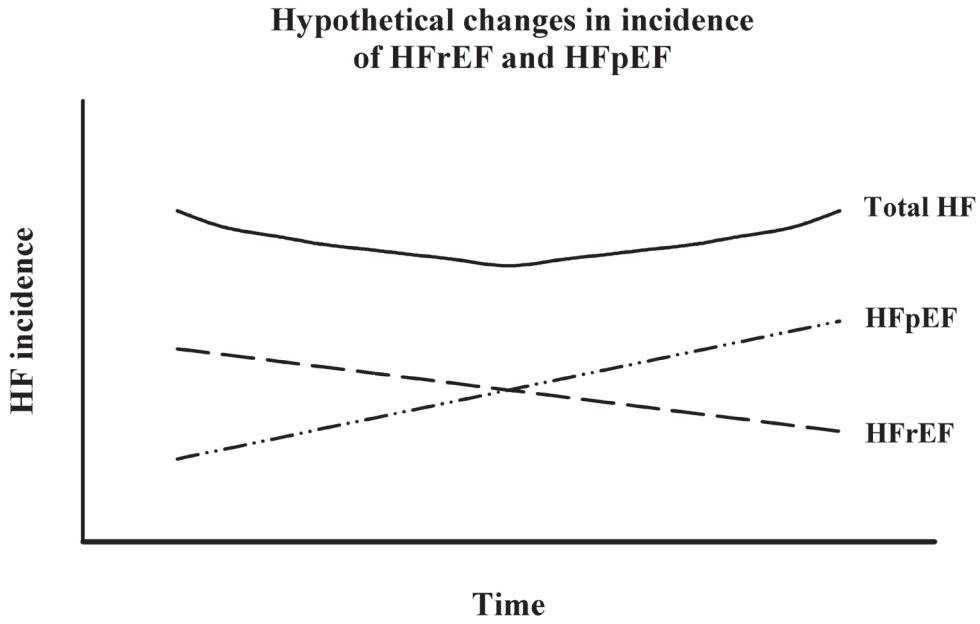


Figure 1 The changing face of heart failure.

for both men and women, but five year survival rate after diagnosis of HF was 48% (45% in women vs. 51% in men; P<0.05), which is still remarkably poor in the current era. Finally, hypertension was the most common cardiovascular co-morbidity, followed by ischemic heart disease, atrial fibrillation and diabetes mellitus, cerebrovascular disease and chronic obstructive pulmonary disease.

Along with the observed decreased HF incidence and improved survival (and previous epidemiologic reports), the prevalence of HF remained stable during the follow-up period. Increased awareness of physicians for HF, improved pharmacological and device treatment are probably responsible for this decrease. The current study also shows valuable epidemiologic data with regard to concomitant diseases associated with HF development (Table 1, Zarrinkoub et al.).[7] Prevalence of all co-morbidities, apart from hypertension, decreased during the follow-up period, which may explain decrease in HF incidence.

These contemporary data are valuable since they provide more insight into the incidence and prevalence of HF in the current time. Also, the investigators examined a large study population and the quality of health registries in Stockholm appears to be high. Nevertheless, the data are limited by the fact that assessment of signs and symptoms of HF from chart review alone

was retrospective, and for example, physical findings of congestion such as jugular distention or subjective complaints of exertional dyspnoea and fatigue are easy to miss in everyday practice. Indeed, HF underrecognition is more common in patients with HFpEF, than in those with HFrEF, as a left ventricular ejection fraction (LVEF) is still very important for many physicians, and in many cases the diagnosis of HF is not considered when LVEF is normal.[8, 9] In other words, the diagnosis of HFpEF is more difficult than the diagnosis of HFrEF, because it is largely one of exclusion, i.e. potential non-cardiac causes of the patient's symptoms (such as anaemia or chronic lung disease) must first be discounted.[1, 6] Also, it has been suggested that a large proportion of patient with new onset HFpEF is mainly seen in the outpatient setting or by the general practitioner, and are therefore not included in hospital registries.

HFpEF vs HFrEF: the changing face of heart failure

In recent years, there is an increasing awareness, that HFpEF is a different condition than HFrEF. Several cut-off values between 40 and 50% of LVEF are proposed, to differentiate between both HF subtypes. A subject at risk for HFpEF is typically an elderly female with hypertension or atrial fibrillation, while males with coronary artery disease (and old myocardial infarction) comprise a typical risk profile for HFrEF.[10, 11] For a long time, it was assumed that prognosis in patients with HFpEF was better than in those with HFrEF,[12] but this may have been due to the fact, that in many HFpEF studies patients were included, that may not really have had HF.[6] Indeed, in the last few years various studies shave shown, that for patients with the same severity of HF (and a similar increase in natriuretic peptides), prognosis is equally poor for HFrEF and HFpEF.[13, 14] The lack of distinguishment between both HF phenotypes makes interpretation of the results of Zarrinkoub and colleagues more difficult. It is clear that HFpEF is becoming more common, both in absolute and in relative numbers.[4, 14, 15] Owan and colleagues have already shown in 2006 that the incidence of hospitalizations for HFpEF was increasing, while this was decreasing for HFrEF during the same follow-up period.[4] More recent studies confirm these findings, including a large study from 275 hospitals in the USA.[15] Importantly, it is suggested that this rise in number of HFpEF patients is yet an underestimation of the true burden of HFpEF. Clinical underrecognition of HFpEF is a current topic, because signs and symptoms tend to be less specific and concomitant co-morbidities

are more common.[6, 14] Recently, a similar observation was made in a large community-based cohort in the Netherlands, where the proportion of patients with new onset HFpEF, compared to new onset HFrEF, was initially relatively low, but there was a catch-up effect later on in the study.[10] The male patient with a previous myocardial infarction is more likely to be included in hospital-based health registries, than the elderly woman with hypertension and/or diabetes.

Thus, with regard to the observed overall decreased incidence of HF presented by Zarrinkoub and colleagues, we speculate this may be caused by a true decrease in new onset HFrEF, whereas the potential underestimated incidence of new onset HFpEF leads to a slightly false postive picture. This hypothesis is actually supported by the development of patient characteristics for prevalent HF in the study by Zarrinkoub. They showed that during follow-up, the prevalence of all concomitant diseases was found to be decreased, except for hypertension, which is the main underlying etiology (together with age) for HFpEF.[10, 11] Considering the aforementioned epidemiologic trends, this might result in increased number of HFpEF in future studies (Figure 1).

In conclusion, Zarrinkoub and colleagues[7] provide an interesting update on the epidemiology of HF in a highly developed European country. The overall decrease in HF incidence suggests successful management of HF and confirms trends from recent epidemiologic studies. However, it should be noted that mainly changes in HFrEF may account for this decrease, while patients with HFpEF may (partly) not have been identified. Importantly, undertreatment of hypertension seems to continue to play an important role here.

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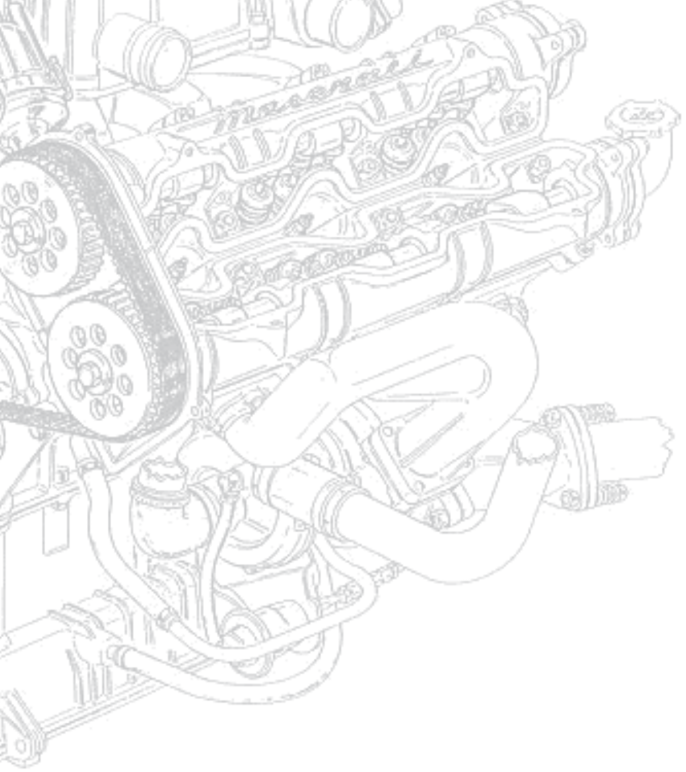

Abstract

The incidence and prevalence of heart failure is increasing, especially heart failure with preserved ejection fraction (HFpEF) relative to heart failure with reduced ejection fraction (HFrEF). For both HFrEF and HFpEF, there is need to shift our focus from secondary to primary prevention. Detailed epidemiologic data on both HFpEF and HFrEF are needed to allow early identification of at-risk subjects. Current cohorts with new onset heart failure lack uniformity with respect to diagnosis, follow-up and population characteristics, but most importantly fail to distinguish between HFpEF and HFrEF. Studies on prevalent heart failure show ischemic heart disease as the predominant risk factor for HFrEF, while hypertension, atrial fibrillation and diabetes are risk factors for HFpEF. As it becomes increasingly clear that both subtypes of heart failure are different syndromes, new cohorts and trials are necessary to obtain separate data on both subtypes of heart failure.

Chapter 2

Comparing heart failure with reduced ejection fraction to heart failure with preserved ejection fraction: an epidemiologic perspective

Frank P. Brouwers
Hans L. Hillege
Wiek H. van Gilst
Dirk J. van Veldhuisen

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Introduction

Heart failure is a major cause of morbidity and mortality in the general population. Its prevalence in the population has increased dramatically over time.[1] The incidence of heart failure is increasing as well, due to both better medical treatment and, most importantly, improved survival rates following preceding cardiovascular disease like myocardial infarction or hypertension.[2-4] Heart failure is affecting men and women in near equal numbers, though women are historically under-represented in clinical HF trials.[5, 6] Regardless of sex, heart failure is typically a disease of the elderly, with an estimated prevalence of heart failure of 23 million people worldwide in 2010.[7] Due to advances in medical care and the exponential increase in lifestyle-related cardiovascular risk factors such as diabetes mellitus (DM), hypertension, obesity and persistently high global prevalence of nicotine use, the prevalence of heart failure in the United States is expected to affect up to 20% of the population by 2040.[2, 8, 9] This will place a large economic burden on national health care systems.[10, 11]

In this context, the need to distinguish heart failure with reduced ejection fraction (HFrEF) from heart failure with preserved ejection fraction (HFpEF) becomes of great importance. The number of hospitalizations for HFpEF has increased over time, compared to a stable admission rate for patients with HFrEF, see Figure 1.[12-14] This has been explained by an increase in the prevalence of risk

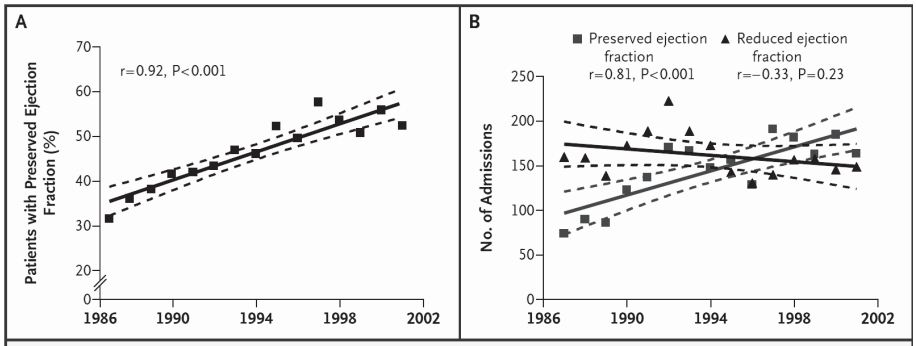

Figure 1. **Secular Trends in the Prevalence of Heart Failure with Preserved Ejection Fraction.**
Panel A shows the increase during the study in the percentage of patients with heart failure who had preserved ejection fraction. Panel B shows that the number of admissions for heart failure with preserved ejection fraction increased during the study period, whereas the number of admissions for heart failure with reduced ejection fraction did not change. The solid lines represent the regression lines for the relation between the year of admission and the percentage of patients with heart failure who had preserved ejection fraction (Panel A) and the number of admissions for heart failure with preserved or reduced ejection fraction (Panel B). The dashed lines indicate 95 percent confidence intervals.

Figure 1 From Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. N Engl J Med 2006; 355:251-9. Reproduced with permission from (scientific reference citation), Copyright Massachusetts Medical Society.

Table 1 Overview of cohorts with new onset heart failure

Cohort	Year	echo	Population	Age*	Pop. size (HF cases)	FUP (yrs)	Criteria for HF
FHS [20]	1971	-	population based	30-62	5192 (142)	16.0	Criteria from the FHS
Coronary artery surgery study[26]	1994	-	stable CAD	51.8	2001 (118)	12.1	Discharge or mortality forms / self -reported
EPESE [25]	1998	68%	community-based	80.0 ± 7.2	2812 (292)	1.0	ICD coding, then case by case review
Rochester Epidemiology Project [37]	1998	63%	population based	median: 45	106470 (216)	5.0	Criteria from the FHS
GP population West London [38]	1999	91%	population based	76.0	150582 (220)	1.7	ESC criteria
CHS [24]	2000	93%	community-based	73 ± 5	5888 (597)	5.5	Case by case validation (event committee)
GP population South London [35]	2001	100%?	population based	unk	292000 (332)	1.3	ESC criteria
KPNW [28]	2001	92.5%	diabetics	63.4 ± 12.0	17076 (1693)	2.5	ICD-9 coding
Rotterdam Study[23]	2002	100%	population based	70	7277 (345)	6.0	Case by case review (cardiologist)
Medicare[27]	2004	-	diabetics	73.8 ± 6.4	115803 (12.6/100yrs)	5.0	ICD-9 coding
Heart and Soul Study[29]	2006	-	stable CAD	67 ± 10	990 (57)	3.1	Hospitalization with HF signs/symptoms
Health ABC study [56]	2008	-	population based	73.6 ± 2.9	2935 (258)	6.5	Criteria from the CHS
Malmo Diet and Cancer Study[36]	2010	-	community-based	57.6 ± 5.9	5187 (112)	13.8	ICD-8/9/10 coding
Framingham Offspring Study [55]	2010	-	population based	58 ± 10	2754 (95)	9.4	Criteria from the FHS
EPIC Norfolk [57]	2011	-	population based	58.1 ± 9.2	20299 (1258)	12.8	ICD-10 coding
ARIC study [31]	2012	-	community-based	54.1 ± 5.6	13660 (1369)	14.9	Hospital discharge register (ICD-9 coding)
Parkinson's patients[30]	2012	-	Parkinson's patients	78.0 ± 7.2	25459 (518)	3.0	Criteria from the FHS

*mean age±standard deviation if present. If unknown, estimated (Italic)

**observational data

HF - Heart failure; EPESE - Established Populations for Epidemiologic Study of the Elderly program; FHS - Framingham Heart Study; EPIC - European Prospective Investigation into Cancer and Nutrition; KPNW - Kaiser Permanente Northwest Division; ARIC - Atherosclerosis Risk in Communities; CHS - Cardiovascular Health Study

factors associated specifically with HFpEF, i.e. DM, hypertension and atrial fibrillation. Moreover, it has become clear that the prognosis of patients with HFpEF is probably as poor as for HFrEF.[4] A complicating factor is the fact that despite a number of potentially favorable reports on treatment with angiotensin converting enzymes inhibitors (ACEi), angiotensin receptor blockers (ARB) and beta-blockers in HFpEF,[15-17] no prospective trial has successfully reduced mortality or re-hospitalization for patients with HFpEF.[18] For both HFrEF and HFpEF, there is need to shift focus from secondary to primary prevention, requiring a thorough understanding of the pathophysiology underlying both types, particularly HFpEF. Studies on the prevalence, incidence and prognosis of heart failure are becoming increasingly available; however, several issues need to be addressed. There is lack of consistency with regard to the diagnosis and validation of heart failure cases,[19] but also regarding results and outcome parameters. More importantly, evidence on the incidence and epidemiology of HFrEF and HFpEF reported separately is minimal. In the ongoing, as yet unsuccessful search for evidence based treatment for HFpEF, it is essential to identify and characterize subjects with new onset HFpEF independently from HFrEF, and regard both types of heart failure as distinct diseases.

Cohorts with incident heart failure

Several cohorts have identified patients with a diagnosis of heart failure during follow-up. Table 1 summarizes these cohorts and refers to the year of first publication. Additional registries with only incidence and / or mortality rates, but no data on clinical characteristics were not taken into account. Reviewing this table raises a number of interesting points.

Most cohorts have been identified during the last decade and are derived from unselected populations. With new technology to aid in the diagnosis of heart failure, this subsequently increased awareness of the problem. This is a promising development and an important first step towards describing typical epidemiologic features of subjects at risk for developing heart failure. However, the criteria used to identify patients and validate a new diagnosis of heart failure are generally inconsistent. These range from criteria from Framingham,[20] the National Health and Nutrition Examination Survey (NHANES)[21] and the European Society of Cardiology,[22] to self-reported heart failure or a hospital discharge diagnosis based on ICD-coding. Although all separate methods to define new onset heart failure are well validated, it makes comparison between these cohorts difficult. In three cohorts, a specialized panel or committee was

assigned to ascertain the diagnosis of new onset heart failure via individual case review.[23-25] The different screening methods for new onset heart failure used in these cohorts usually result in high specificity, with no false positive cases of new onset heart failure. On the other hand, heart failure incidence rates are likely underestimated, as patients with signs and symptoms associated with heart failure who were not hospitalized will not have been detected. True incidence rates for new onset heart failure will therefore probably be higher.

Another interesting observation is that there are broad differences in population characteristics, which also make comparison of results between cohorts difficult. Mean age ranges from mid-fifties[26] to octogenarian subjects[25] and several cohorts consist of specifically selected subjects with diabetes, stable coronary artery disease or even Parkinson's patients.[26-30] There are also considerable differences in enrollment of subjects with different racial backgrounds between cohorts. The proportion of black men and women ranges from 12 to 25%,[24, 27, 29, 31] however it is not described in the majority of cohorts. Many large studies have already shown that the incidence of heart failure is substantially higher among blacks than among whites, especially among younger adults.[32, 33] These racial differences are largely explained by known clinical risk factors, such as hypertension and DM,[34] nonetheless inclusion of subjects with different racial backgrounds could bias results. Lastly, there is large variation in follow-up duration, from studies with one year follow-up to those with over ten years.[20, 25, 35, 36]

Finally, Table 1 illustrates that in the large majority of cohorts, no data is available on LVEF. This is an essential limitation, making the distinction between HFrEF and HFpEF impossible. Additionally, studies in which echo data is available have a low number of new onset heart failure cases or relatively short follow-up.[37, 38] Compounding the issue, there is currently no consensus in the literature regarding a precise cut-off value for LVEF in the diagnosis of HFpEF versus HFrEF. While both Senni et al and Cowie et al use an LVEF cut-off of ≥50%,[37, 38] studies with prevalent heart failure patients have used cut-off values ranging from 35 to 55%.[22] The new 2012 heart failure guidelines from the European Society of Cardiology advise that a LVEF below 50% should be considered reduced.[22]

HFpEF versus HFrEF

It is estimated that about half of all patients presenting with heart failure have a preserved LVEF.[39] Several retrospective cohort studies have shown clinical differences between patients with prevalent HFpEF and HFrEF, which

underscores the necessity for considering each subtype of heart failure a distinct disease. At first clinical presentation, patients with HFpEF are older, more often female and obese than those with HFrEF. Furthermore, they are less likely to have coronary heart disease and more likely to have hypertension and atrial fibrillation.[40-42] On the other hand, patients with HFrEF are more likely to have a history of ischemic heart disease, defined as either prior myocardial infarction or ECG abnormalities. Other risk factors which have been associated with HFrEF are DM and history of alcohol abuse.[1, 8, 43] Renal failure is also a frequently occurring condition in both HFrEF and HFpEF, the so-called cardiorenal syndrome.[44] Some studies have shown evidence of renal dysfunction being a more significant risk factor for new onset HFpEF than for new onset HFrEF[45, 46] by measuring cystatin C or urinary albumin excretion.[47, 48]

Mortality remains very high after the onset of symptoms,[49-51] although long-term mortality rates have improved over time.[52] Several studies have shown equal mortality rates for patients with HFpEF and HFrEF.[53, 54] Cause of death in patients with HFpEF is more often non-cardiovascular than in HFrEF patients, who have higher cardiovascular mortality. Furthermore, patients with HFrEF are at higher risk of sudden death compared to HFpEF patients. The TIME-CHF study also showed that patients who died experienced a median of four adverse events and one hospitalization within 60 days prior to death.[53]

As mentioned earlier, current data on patient characteristics for new onset HFpEF compared to new onset HFrEF in a general, unselected population is limited. Two studies of incident cases of HFpEF have associated female gender and older age with increased risk for developing HFpEF.[37, 38] Also, a diagnosis of HFpEF was more likely in an out-patient setting. Typical signs of heart failure, such as cardiomegaly and pulmonary edema, were less apparent and atrial fibrillation was more frequently present in patients with new onset HFpEF. A recent publication by the Framingham Heart Study also shows patient characteristics for both subtypes of heart failure.[41] In 712 subjects with new onset heart failure, 46% were diagnosed with HFpEF, with a LVEF cut-off of 45%. Multiple patient characteristics at the time of initial heart failure presentation and pre-onset patient characteristics differed between participants with new onset HFpEF and HFrEF. Female gender and atrial fibrillation were independently associated with an increased risk for HFpEF, while presence of coronary heart disease, increased heart rate and potassium, and ischemic abnormalities on the electrocardiogram were associated with an increased risk

for HFrEF.[41] Several clinical traits differed in prevalence across the spectrum of LVEF, suggesting that HFpEF and HFrEF are overlapping clinical syndromes. As the authors conclude, more studies defining cases with new onset heart failure are necessary to further define separate risk factor profiles for HFpEF and HFrEF. This would allow identification of subjects at risk for developing heart failure and could lead to targeted preventive efforts.

Epidemiologic Perspectives

Multiple studies have reported on epidemiologic characteristics of subjects with new onset and prevalent heart failure. However, studies distinguishing between new onset HFrEF and HFpEF are necessary, as both subtypes of heart failure should be considered different syndromes. There is increasing evidence that incidence rates of HFpEF are equal to HFrEF and that prognosis is equally poor. However, in contrast to HFrEF, there is currently no evidence based treatment for HFpEF.[18] Along with the fact that hospitalizations for HFpEF are increasing relative to HFrEF,[14] the burden of HFpEF on health care systems will expand exponentially in the near future. While most studies have reported on specific risk factors for overall new onset heart failure, like older age, increased NT-proBNP or urinary albumin creatinine ratio,[36, 55] there is need for new studies presenting data on new onset HFrEF versus new onset HFpEF. Detailed epidemiologic data for subjects with new onset heart failure, compared to healthy subjects with no diagnosis of heart failure during follow-up are still lacking. Furthermore, clinical and biochemical characteristics with predictive capabilities for new onset HFpEF, in contrast to HFrEF, have also not been identified. The Framingham Heart Study has shown different clinical profiles before first clinical presentation; however the mean time from baseline to time of diagnosis is short. For effective preventive strategies, early identification of subjects at risk for developing heart failure is necessary to start treatment in an early stage.

Conclusions

HFrEF and HFpEF are two different cardiovascular syndromes and both require a different approach. Ischemic heart disease remains the main cause for HFrEF, while atrial fibrillation, female gender and ageing are risk factors for HFpEF. However, more studies on the epidemiology of both specific types of new onset heart failure are necessary for early identification, risk stratification and preventive treatment.

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Abstract

AIMS: Differences in clinical characteristics and outcome of patients with established heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) are well established. Data on epidemiology and prediction of new onset HFpEF, compared with HFrEF have not been described.

METHODS AND RESULTS: In 8,592 subjects of the Prevention of REnal and Vascular ENdstage Disease (PREVEND), a community-based, middle-aged cohort study, we performed cause-specific hazard analyses to study the predictive value of risk factors and established cardiovascular biomarkers on new onset HFrEF versus HFpEF (left ventricular ejection fraction ≤40% and ≥50%, respectively). A P-value for competing risk (P_{cr}) <0.10 between HFrEF and HFpEF was considered statistically significant. All potential new onset heart failure cases were reviewed and adjudicated to HFrEF or HFpEF by an independent committee. During a median follow-up of 11.5 years, 374 (4.4%) subjects were diagnosed with heart failure, of which 125 (34%) HFpEF and 241 (66%) HFrEF. The average time to diagnosis of new onset HFrEF was 6.6±3.6 years and 8.3±3.3 years for HFpEF (P <0.001). Male gender was associated with new onset HFrEF, while female gender with new onset HFpEF (P_{cr} <0.001). Higher age and increased NT-proBNP increased the risk for both HFpEF and HFrEF, although for age this was stronger for HFpEF (P_{cr} =0.018), while NT-proBNP was stronger associated with risk for HFrEF (P_{cr} =0.083). Current smokers, increased hs-TnT and previous myocardial infarction conferred a significantly increased risk for HFrEF, but not for HFpEF (P_{cr} =0.093, 0.091, 0.061, respectively). Conversely, a history of atrial fibrillation, increased urinary albumin excretion and cystatin C were significantly more associated with the risk for HFpEF, but not with HFrEF (P_{cr} <0.001, 0.061 and 0.033, respectively). The presence of obesity at baseline was associated with comparable prognostic information for both HFpEF and HFrEF.

CONCLUSION: Higher age, urinary albumin excretion, cystatin C and history of atrial fibrillation are strong risk factors for new onset HFpEF. This underscores differential pathophysiologic mechanisms for both subtypes of heart failure.

Chapter 3A

Incidence and epidemiology of new onset heart failure with preserved versus reduced ejection fraction in a community-based cohort: 11 year follow-up of PREVEND

Frank P. Brouwers
Rudolf A. de Boer
Pim van der Harst
Adriaan A. Voors
Ron T. Gansevoort
Stephan J. Bakker
Hans L. Hillege
Dirk J. van Veldhuisen
Wiek H. van Gilst

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Introduction

Heart failure is a progressive syndrome with high morbidity and mortality despite recent improvements of its treatment.[1, 2] Due to the ageing population, it is expected that the incidence and prevalence of heart failure will increase exponentially in the next decade.[3] Preventing new onset heart failure is increasingly important and requires knowledge of its risk factors.[4,5] Several studies have established risk factors for new onset heart failure, including higher age, hypertension and the presence of ischemic heart disease.[6-8] Initially, studies aimed at identifying risk factors were based on a heart failure diagnosis on signs and symptoms only.[3, 9] More recently, the diagnosis of heart failure was defined by reduced left ventricular ejection fraction (LVEF), with or without symptoms.[4, 7] We now recognize two subtypes of heart failure: heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF). Data on the incidence of new onset HFpEF and its risk factors in population based cohorts are scarce and studies directly comparing new onset HFpEF versus HFrEF are lacking.

In a community-based cohort, we identified all cases of new onset heart failure during 11 years of follow-up and adjudicated them as either HFrEF or HFpEF. Using available clinical and biochemical baseline characteristics, we identified risk factors for new onset HFpEF and HFrEF.

Methods

Study population

The study was performed using data of the PREVEND cohort study, which has been described elsewhere.[10, 11] In summary, from 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (N = 85,421) were asked to send in a first morning urine sample and complete a short questionnaire on demographics and cardiovascular disease history and 40,856 subjects responded (47.8%). All subjects with urinary albumin excretion (UAE) ≥10 mg/l (N = 7,786) in their morning urine as well as a randomly selected control group with a UAE <10 mg/l (N = 3,395) were invited to an outpatient clinic for detailled assessment of cardiovascular and renal risk factors, including filling in questionaires, measuring anthropometrics, and blood and urine sampling. After excluding subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects unable or unwilling to participate, a total of 8,592 subjects completed the screening program. The PREVEND study was approved

by the institutional medical ethics committee and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Definitions

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits, using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure >140mmHg, diastolic blood pressure > 90mmHg or self-reported use of antihypertensive medication. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2) and obesity was defined as a BMI > 30kg/m^2. Hypercholesterolemia was defined as total serum cholesterol > 6.5 mmol/l (251 mg/dl) or a serum cholesterol > 5.0 mmol/l (193 mg/dl) if a history of myocardial infarction (MI) was present or when lipid-lowering medication was used. Type 2 diabetes was defined as a fasting plasma glucose >7.0 mmol/l (126 mg/dl), a non-fasting plasma glucose >11.1 mmol/l or use of anti-diabetic drugs. UAE was calculated as the average value from two

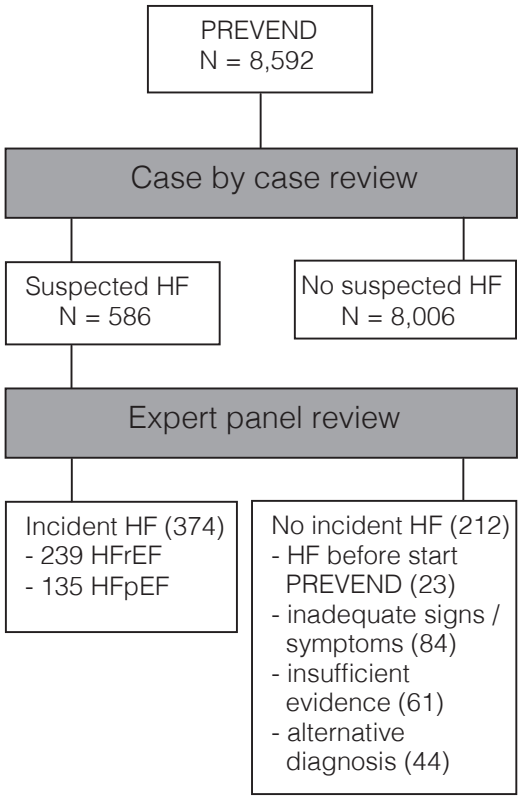


Figure 1 Flowchart of identification and validation of subjects with new onset heart failure

consecutive 24h urine collections. The glomerular filtration rate (eGFR) was estimated using the simplified Modification of Diet in Renal Disease (sMDRD) formula.[12] Smoking was defined as current nicotine use or quit smoking within the previous year. History of MI was defined as participant-reported hospitalization for at least 3 days as a result of this condition. Standard 12-lead electrocardiograms were recorded using the computer program Modular ECG Analysis System (MEANS),[13] and AF was defined according to Minnesota codes 8.3.1 and 8.3.3.

Assays

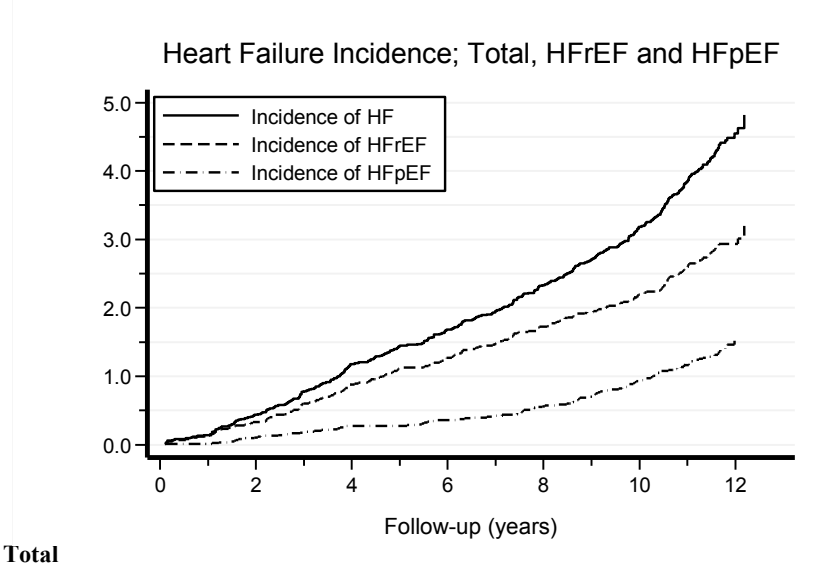
At baseline, EDTA plasma samples were drawn from all participants for biomarker assessment. Aliquots of these samples were stored immediately after collection at -80°C until analyses. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and highly-sensitive C-reactive protein (hs-CRP) were measured, as described in detail elsewhere.[14, 15] Highly-sensitive troponin T (hs-TnT) was measured using Modular Analytics serum work areas, with <10% coefficient of variation at the 99th percentile of the reference range (Roche Diagnostics). Urinary albumin concentration was determined by nepholometry, with a threshold of 2.3 mg/l and intra- and interassay coefficients variation of 2.2 and 2.6%, respectively (BNII, Dade Behring Diagnostica, Marburg, Germany).

Heart failure and cardiovascular events

Follow-up for the present investigation was defined as time between the baseline visit to the outpatient department and the date of new onset heart failure, or 01 January 2010. Subjects were censored at the date they moved to an unknown destination or at the last date of follow-up (01 January 2010), whatever date came first. Information on dates and causes of death for every participant were obtained from Statistics Netherlands[16] and coded according to the 10th revision of the International Classification of Diseases (ICD).

The patient population of PREVEND, from the city of Groningen, has a low migration rate[16] and is covered by two main hospitals in the region. Patient files were checked in both hospitals for presence of heart failure at baseline and for new onset heart failure, by recording signs, symptoms and objective evidence of heart failure. Permission to access hospital records was granted by the local Ethics Committees of both hospitals. Using criteria in accordance to the Heart Failure Guidelines of the European Society of Cardiology (ESC),[17, 18]

586 individual cases were identified as suspected heart failure, as shown in Figure 1. An endpoint adjudication committee of seven independent experts in the field of heart failure, evaluated all cases suspected for the diagnosis of new onset heart failure. Each case was validated by two different experts by reviewing anonimized clinical charts, hospitalization and physician office records in order to ascertain the incidence of heart failure. In case of consensus, patients were classified as "definite new onset heart failure", "definite no new onset heart failure" or "definite heart failure, with date of onset before time of recruitment in PREVEND". In case of difference of opinion about an individual case, the committee made a joint decision. Based on LVEF at the time of diagnosis, heart failure was classified as HFrEF or HFpEF (LVEF ≤40% or ≥50%, respectively). The cut-offs were chosen due to the lack of consensus in the most recent ESC guidelines for diagnosis of new onset heart failure.[17, 18] Subjects in the grey area, with a LVEF 41-49% (N = 8), were excluded from the analyses to prevent blending and dilution of differential epidemiological profiles. The etiology and date of onset of heart failure was also derived from clinical charts. Data on LVEF were available in 98.4% of cases with new onset heart failure. In six cases, diagnosis was confirmed through joint decision, because of insufficient data on LVEF.



Total							
HF	8569	8313	7966	7638	7312	6633	1273
HFrEF	8569	8322	7991	7669	7351	6693	1287
HFpEF	8569	8336	8031	7721	7412	6747	1306

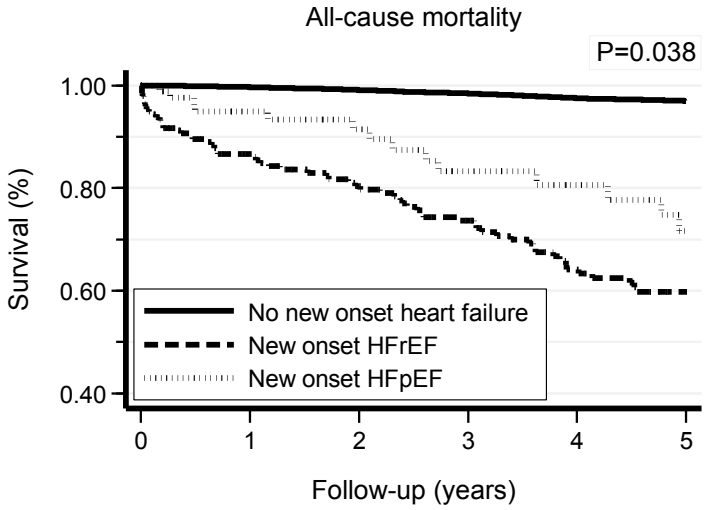
Figure 2 Cumulative incidence of new onset heart failure, divided by total new onset heart failure, heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. Incidence of heart failure is adjusted for mortality during follow-up.

Table 1 Baseline characteristics of subjects without heart failure during the follow-up and of subjects with new onset heart failure during the follow-up*

	No HF N=8195	HF** N=374	P-value	HFrEF N=241	HFpEF N=125	P-value
Demography						
Age (yrs)	49±12	62±10	<0.001	62±10	63±9	0.340
Males (%)	49.2	64.4	<0.001	73.4	48.0	<0.001
Caucasians (%)	95.4	97.3	0.187	97.5	97.6	0.999
BMI (kg/m^2)	26±4	28±5	<0.001	28±4	29±5	0.060
>30 (%)	14.9	30.21	<0.001	29.1	32.0	0.559
Systolic BP (mmHg)	128±20	147±23	<0.001	145±22	149±25	0.120
Diastolic BP (m mHg)	74±10	80±10	<0.001	80±10	79±9	0.202
Heart rate (bpm)	69±10	70±12	0.070	70±12	70±12	0.604
Baseline medical history						
Smoking or quit <1 year (%)	38.0	38.2	0.928	43.5	28.8	0.006
Myocardial infarction (%)	5.1	25.6	<0.001	28.8	19.5	0.056
Hypertension (%)	30.1	71.1	<0.001	68.1	75.8	0.123
Hypercholesterolemia (%)	25.5	47.0	<0.001	48.3	42.2	0.271
Diabetes Mellitus (%)	3.4	12.3	<0.001	12.0	12.2	0.950
Atrial fibrillation (%)	1.0	4.6	<0.001	4.6	5.0	0.880
Laboratory values						
Glucose (mmol/l)	4.9±1.1	5.5±1.9	<0.001	5.4±1.7	5.6±2.1	0.355
Cholesterol (mmol/l)	5.6±1.1	6.0±1.0	<0.001	6.0±1.0	6.0±1.0	0.910
HDL (mmol/l)	1.33±0.40	1.22±0.36	<0.001	1.20±0.36	1.27±0.35	0.085
Triglicerides (mmol/l)	1.15 (0.84-1.67)	1.39 (1.00-1.93)	<0.001	1.41 (0.97-2.03)	1.36 (1.01-1.78)	0.567
Serum Creatinine (umol/l)	82 (73-92)	87 (76-99)	<0.001	90 (80-102)	81 (72-97)	<0.001
eGFR (ml/min/1.73m^2)	81±15	75±16	<0.001	75±14	75±18	0.727
<60 (%)	6.0	12.7	<0.001	12.9	12.9	0.997
Cystatin C (mg/l)	0.77 (0.69-0.87)	0.89 (0.79-1.03)	<0.001	0.91 (0.79-1.05)	0.88 (0.77-1.04)	0.218
UAE (mg/24h)	9.2 (6.3-16.9)	19.4 (9.3-52.2)	<0.001	19.2 (9.3-50.8)	20.4 (9.9-57.8)	0.576
hs-CRP (mg/l)	1.24 (0.54-2.88)	2.47 (1.18-4.83)	<0.001	2.48 (1.24-4.83)	2.05 (0.88-4.46)	0.141
NT -proBNP (ng/l)	36 (16-70)	104 (43-285)	<0.001	121 (45-358)	86 (37-172)	0.014
hs-TnT (ng/l)	2.5 (2.5-4.0)	7.0 (4.0-10.0)	<0.001	7.0 (4.0-11.0)	5.0 (3.0-9.0)	0.001

* Continuous variables are presented as mean+standard deviation and compared with the use of Student's t-test, in case of normal distribution. In case of skewed distribution, continuous variables are presented as median (interquartile range) and compared using the Kruskall-Wallis test. Binary categorical variables were compared using standard Chi-squared tests. HF denotes heart failure, BMI body-mass index, BP blood pressure blood pressure, HDL high density lipoprotein, hs-CRP highly-sensitive C-reactive protein, NT-proBNP N-terminal pro-B-type natriuretic peptide, hs-TnT highly-sensitive troponin T, eGFR estimated glomerular filtration rate, and UAE urinary albumin excretion

** mean time to diagnosis =7.2 (±3.6) years



Number at risk						
No new onset heart failure	8195	8139	7977	7842	7696	7547
New onset HFrEF	196	144	122	104	75	62
New onset HFpEF	86	64	48	36	28	23

Figure 3 Five year survival curve after diagnosis of new onset heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

Statistical analysis

By design, the PREVEND study overselected subjects with an elevated UAE (≥10mg/l). It should be clear that this is not a random sample of a general population, where all elementary units have an equal probability of being selected. Statistical formulas to calculate population parameter estimates should be used to account for the likelihood of selection. A design-based analysis was performed to overcome this overselection of subjects with elevated UAE. This statistical weighting method allows conclusions to be generalized to the general population.[15, 19] Baseline continuous data are reported as mean (standard deviation) for normal data. NT-proBNP, hs-TnT, UAE, cystatin C, serum triglycerides and hs-CRP showed a log-linear functional shape with the response variable and were transformed to a 2-log scale and reported as median (interquartile range). This means that risk estimates should be interpreted as the relative risk if values were doubled (e.g. 1 to 2 mg/l or 10 to 20 mg/24h). We fitted Cox proportional hazards models to the data and the Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. For multivariate regression analysis, we imported variables which reached significance (P<0.10) in univariate analysis. Two competing endpoints were distuingished: HFrEF and HFpEF. All

Table 2 Cox Regression: Cause Specific Hazard (Risk) Ratios

	Adjusted for Age and Sex		Mutually adjusted*		HFrEF	HFpEF	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	HR (95% CI)	P_{cr}**
Age (per 10yrs)	-	-	1.81 (1.47-2.24)	<0.001	1.61 (1.24-2.09)	2.53 (1.93-3.30)	0.018
Males	-	-	1.48 (1.03-2.13)	0.035	2.43 (1.49-3.95)	0.56 (0.31-1.01)	<0.001
Obesity	1.93 (1.37-2.73)	<0.001	1.62 (1.10-2.37)	0.014	-	-	0.750
Heart rate (per 5bpm)	1.05 (0.98-1.13)	0.155					
Hypertension	1.99 (1.37-2.89)	<0.001	1.17 (0.77-1.77)	0.458	-	-	0.288
Myocardial infarction	3.45 (2.38-4.99)	<0.001	2.27 (1.54-3.34)	<0.001	2.77 (1.73-4.43)	1.25 (0.64-2.45)	0.058
Smoking or quit smoking <1year	1.31 (0.96-1.79)	0.087	1.24 (0.87-1.77)	0.228	1.51 (0.96-2.36)	0.80 (0.46-1.41)	0.086
Atrial Fibrillation	2.64 (1.23-5.66)	0.013	1.10 (0.55-2.19)	0.787	0.42 (0.19-0.93)	3.79 (1.64-8.77)	<0.001
Diabetes Mellitus	2.41 (1.51-3.85)	<0.001	1.66 (0.99-2.78)	0.056	-	-	0.794
Hypercholesterolemia	1.65 (1.21-2.26)	0.002	1.34 (0.95-1.88)	0.096	-	-	0.713
logCreatinine (per doubling)	1.00 (0.84-1.20)	0.973					
eGFR >60ml/min/1.73m^2	1.07 (0.66-1.74)	0.782					
logCystatin C (per doubling)	1.43 (1.23-1.68)	<0.001	1.08 (0.94-1.24)	0.295	0.98 (0.86-1.11)	1.45 (1.03-2.04)	0.033
logUAE (per doubling)	1.35 (1.22-1.50)	<0.001	1.01 (0.91-1.14)	0.798	0.96 (0.84-1.09)	1.21 (0.98-1.48)	0.061
logHs-CRP (per doubling)	1.41 (1.17-1.70)	<0.001	1.14 (0.92-1.41)	0.228	-	-	0.230
logNT -proBNP (per doubling)	2.11 (1.79-2.49)	<0.001	1.68 (1.39-2.04)	<0.001	1.85 (1.42-2.41)	1.35 (1.06-1.72)	0.082
logHs-TnT (per doubling)	1.67 (1.51-1.86)	<0.001	1.33 (1.17-1.52)	<0.001	1.38 (1.18-1.60)	1.10 (0.90-1.36)	0.091

Univariate and multivariate endpoint: Total incident HF. All variables from multivariate regression are tested for competing risk between HFrEF and HFpEF. Obesity denotes body mass index >30kg/m^2, HDL-cholesterol high density lipoprotein cholesterol, eGFR estimated glomerular filtration rate, UAE urinary albumin excretion, hs-CRP highly-sensitive C reactive protein, NT-proBNP N-terminal pro-Brain-type natriuretic peptide, hs-TnT highly-sensitive troponin T

* Adjusted for age, sex and all variables from the univariate analyses with a P-value <0.10.

** P_{cr}=P-value for competing risk: heart failure with reduced vs. preserved ejection fraction.

variables from the multivariate analyses were explored using cause-specific hazard analyses, which allowed us to compare effects of explanatory variables on either HFrEF or HFpEF. To control for the type I error in the cause-specific hazard analysis (effect-by-covariate), and increasing power for the analysis, a P-value for competing risk (P_{cr}) between HFrEF and HFpEF of <0.10 is considered statistically significant.[20, 21] Results are summarized as hazard (risk) ratios, with 95% confidence intervals based on robust standard error estimates. A value of P<0.05 (2-sided) was used as the nominal level of statistical significance. Individual relative hazards were estimated by post-estimation, based on the multivariate cause-specific cox proportional hazard analysis. To define the proportion of usable subject pairs in which outcome and prediction are concordant, we calculated the Harrell´s C coefficient, for the model for HFpEF and the model for HFrEF. Time to first event was estimated using cumulative incident curves, for total new onset heart failure and both subtypes and adjusted for mortality during follow-up. All analyses were performed using StataIC (version 11.0 software for Windows).

Results

During a median follow-up of 11.5 years (range 10.8-11.9), 374 individuals (4.4%) were diagnosed with new onset heart failure, of whom 125 (34%) were classified as HFpEF and 241 (66%) as HFrEF. The average time to diagnosis of new onset heart failure was 7.2 (±3.6) years; for HFrEF this was 6.6 (±3.6) years and 8.3 (±3.3) years for HFpEF (P<0.001). Figure 2 shows the cumulative incidence of new onset heart failure and separately for HFrEF and HFpEF. Five-year all-cause mortality was higher for subjects diagnosed with new onset HFrEF, compared to new onset HFpEF (P=0.038), as depicted in Figure 3. Baseline characteristics are presented in Table 1 for subjects without heart failure during follow-up and for subjects with new onset heart failure during follow-up. At baseline, subjects who developed heart failure during follow-up were older, more likely male, had higher BMI, blood pressure and heart rate, worse renal function and more likely to have CV risk factors: i.e. hypertension, diabetes and hypercholesterolemia (Table 1). Glucose, total cholesterol, UAE, NT-proBNP, hs-TnT, cystatin C and hs-CRP were also higher at baseline for subjects with new onset heart failure (all P <0.001). Table 1 also shows baseline characteristics for subjects with new onset HFrEF and HFpEF. Subjects with HFrEF during follow-up were more likely male, more smokers and had higher levels of creatinine, NT-proBNP and hs-TnT at baseline. During the follow-up period, there were 169 myocardial infarctions. In 25.4% of subjects, this was followed by new onset HFrEF (N = 37) or HFpEF (N = 6).

Associations of clinical and biochemical characteristics with HFpEF and HFrEF

Table 2 summarizes the results of the Cox proportional hazard analysis and the cause-specific hazard analysis. Adjusted for age and gender, the presence or absence of obesity, hypertension, previous MI, atrial fibrillation, diabetes mellitus and hypercholesterolemia was significantly associated with new onset heart failure. Also, higher levels of UAE, hs-CRP, cystatin C, NT-proBNP and hs-TnT were associated with higher risk for new onset heart failure. In multivariate analysis, age, male gender, obesity, previous MI, increased NT-proBNP and hs-TnT remained associated with an increased risk for new onset heart failure. Presence of diabetes and hypercholesterolemia at baseline showed a trend for increased risk for new onset heart failure, when multivariately adjusted (P=0.056 and 0.096, respectively). The Harrell's C coefficient for the model with total new onset heart failure was 0.87 (95% CI 0.84-0.90).

Cause-specific hazard analyses were performed to analyze possible competing risk between the two endpoints (HFrEF and HFpEF). There was a highly significant interaction between HFrEF and HFpEF for gender, indicating that male gender is associated with new onset HFrEF, while female gender is associated with new onset HFpEF (P_{cr}<0.001). Higher age and increased NT-proBNP predicted both new onset HFpEF and HFrEF, although for age this was significantly stronger for HFpEF (P_{cr} = 0.018), while for NT-proBNP this was significantly stronger for HFrEF (P_{cr} = 0.083). In addition, smokers, an increased hs-TnT and subjects with previous MI had a significantly increased risk for HFrEF, but not for HFpEF (P_{cr} = 0.086, P_{cr} = 0.091, P_{cr} = 0.058, respectively). History of atrial fibrillation, increased UAE and cystatin C were significantly more associated with the risk for HFpEF, but not with HFrEF. The presence of obesity at baseline was associated with comparable prognostic information for both HFpEF and HFrEF. Furthermore, the additional value of subjects categorized to values of hs-TnT below the detection limit (N = 4,728) was not significant in the cause-specific hazard model for HFrEF, nor for HFpEF (P_{cr} = 0.493). The proportionality assumptions in the model were satisfied (Chi-squared test 36.05; P=0.141). For both HFrEF and HFpEF, two separate models were created, consisting of the significant variables from the above cause-specific Cox proportional hazard analysis. The model for HFpEF

had a Harrell's C coefficient of 0.90 (95% CI 0.87-0.92) and the model for HFrEF a Harrell's C coefficient of 0.88 (95% CI 0.84-0.91).

Discussion

The present study reports on detailed epidemiologic data on the comparison of new onset HFpEF versus HFrEF. Using a population-based cohort, we report a total incidence of new onset heart failure of 4.4% after 11.4 years of follow-up. Presence of obesity was a common risk factor for incidence of both subtypes of heart failure. Particular strong predictors for HFpEF were older age, female gender, atrial fibrillation, higher cystatin C and UAE. In contrast, male gender, previous myocardial infarction, smoking, hs-TnT and NT-proBNP were significant predictors specifically for HFrEF. This underscores differential pathophysiologic mechanisms for both subtypes of heart failure.

Incidence of heart failure

In this population-based cohort study, we identified 374 patients with a certain diagnosis of new onset heart failure. For this, we used the Heart Failure Guidelines from the ESC and each suspected case was validated by an expert committee. To prevent blending and dilution of epidemiologic profiles between HFrEF and HFpEF, we excluded eight subjects in the so-called grey area of LVEF 41-49%. In sub-analyses with strict cut-off values of 40% or 50%, results are similar to the current analyses. However, the current paper aims to identify differential epidemiologic risk profiles in contrast to evaluating the ideal cut-off for LVEF. By excluding subjects in the grey area of LVEF 41-49%, we present subjects with true new onset HFrEF and HFpEF. In contrast to other epidemiologic studies of new onset heart failure, there was no pre-selection during the screening process, with all 8,952 subjects of PREVEND being individually evaluated for suspected heart failure. Through this method we achieved a very limited underreporting of new onset heart failure in our cohort and no false-positives. Also, data on LVEF were available for almost all cases (98.4%) to accomplish accurate adjudication to HFrEF of HFpEF. Compared to other cohorts with new onset heart failure in the community, the incidence rate of heart failure cases is slightly higher, especially given the young mean age of subjects at baseline (49±12 years) in PREVEND. For example, Smith et al. and Velagaleti et al. report an incidence rate of 2.2% during 14 years of follow-up (mean age at baseline 58 years) and 3.4% during 9.4 years of follow-up (mean age at baseline 59 years), respectively.[5, 22] However, the incidence of HFpEF compared to HFrEF

(34% vs. 66%, respectively) is slightly lower, compared to other community-based studies.[2, 23] It is most likely that the lower average age at baseline in the current study is responsible for this relatively low proportion of subjects with new onset HFpEF. The incidence of HFpEF is presumed to increase during prolonged follow-up. Despite lower age at baseline, through our thorough screening methods for identifying new onset heart failure we achieved accurate and true incidence rate for new onset heart failure in a population-based middle-aged cohort.

Clinical characteristics of new onset heart failure

Few studies have presented data on new onset heart failure in the community and especially studies regarding separate data for HFpEF and HFrEF are lacking.[5, 22] Next to a multimarker strategy for the prediction of new onset heart failure, these studies have reported on specific risk factors for overall new onset heart failure, for example age, NT-proBNP, diabetes and urinary albumin creatinine ratio. Data on HFrEF and HFpEF separately is available from the Rochester Epidemiology Project and the Framingham Heart Study.[23-25] However, the Rochester Epidemiology Project has few cases of new onset heart failure with known LVEF (N = 137), and no biochemical data. It was shown that female sex and age >90years were associated with HFpEF, while left bundle-branch block and myocardial infarction pattern on the ECG were associated with HFrEF.[24] The Framingham Heart Study has one of the largest cohorts with new onset heart failure (N = 534) and reports on the same predictors for HFrEF and HFpEF as the Rochester Epidemiology Project, with the addition of atrial fibrillation for HFpEF.[25] A recent paper by Ho et al. shows discriminating baseline characteristics of patients with new onset heart failure, for HFrEF compared to HFpEF.[23] Multiple risk factors were associated with overall incident heart failure, where age, gender and prior MI acted as effect modifiers between risk for HFrEF and HFpEF. However, epidemiologic data of cases with new onset heart failure in the Rochester Epidemiology Project is evaluated at time of diagnosis, or shortly before diagnosis and presented as odds ratios. Furthermore, important biochemical data is missing in the Framingham Heart Study, including for instance NT-proBNP, hs-TnT. We add to previous investigations by describing detailed epidemiologic data, both clinical as well as biochemical data for new onset heart failure compared to healthy subjects with no diagnosis of heart failure during follow-up. With a mean time from baseline to new onset heart failure of 7.2 years in our cohort, our data adds unique

information on the incidence and the risk factors of both HFpEF and HFrEF and the existence of different risk profiles, many years before symptoms of heart failure become manifest.

We confirm earlier findings of significant risk factors for new onset heart failure, namely higher age, obesity, previous myocardial infarction, NT-proBNP and hs-TnT. Presence of hypertension, diabetes and hypercholesterolemia was however, unlike other studies, not associated with increased risk for new onset heart failure. This could be caused by the definitions utilized in PREVEND, where subjects were also classified as such if treated for the disease. However, a proxy of hypertension, UAE, was significantly associated with new onset HFpEF. Also, hypertension is a major risk factor for atrial fibrillation, another predictor for HFpEF. We add to previous published data, when regarding HFpEF and HFrEF separately. Older females with a history of atrial fibrillation, increased UAE or cystatin C, should be considered specifically at risk for developing HFpEF. Males with a previous myocardial infarction, smoking and increased levels of NT-proBNP or hs-TnT have increased risk specifically for new onset HFrEF.

Biomarkers

Biomarkers provide important information on disease etiology and clinical risk. In the current analyses, we did not use a multimarker approach to identify subjects at risk, but we took the strongest biomarker for different pathophysiologic domains: NT-proBNP, hs-TnT, hs-CRP and cystatin C. Except for NT-proBNP, there are currently no biomarkers registered to aid in early diagnosis of heart failure.[17] This is especially relevant for HFpEF, where diagnosis is more difficult to make.[18, 26] Our data show that NT-proBNP and hs-TnT were associated with new onset HFrEF. For new onset HFpEF however, cystatin C and NT-proBNP (although less strong than for HFrEF) were strong predictors. NT-proBNP, as a marker of myocardial wall stress, thus remains a powerful biomarker for identifying subjects at risk for either subtype of new onset heart failure. The value of hs-TnT in predicting incident heart failure has been described in older adults, but not for either HFrEF or HFpEF specifically.[27] Our data show increased risk for new onset HFrEF, but not HFpEF, which indicates an early trend towards an ischemic etiology. Specifically, an increased hs-TnT could be reflecting increased

risk for developing myocardial infarction, which in turn increases the risk for HFrEF. A decreased kidney function, as determined by cystatin C, has been shown to be associated with left ventricular hypertrophy,[28, 29] vascular stiffness,[30, 31] and new onset heart failure.[32, 33] This is in accordance with our findings, which associate higher levels of cystatin C with an increased risk for developing new onset HFpEF, while there was no increased risk for new onset HFrEF. In a study by Moran et al.[33], cystatin C was associated with both new onset HFpEF and HFrEF, although the levels of cystatin C in their cohort were much higher, probably due to selection of older subjects. This may indicate that in asymptomatic subjects, cystatin C could be an interesting marker for early cardiovascular disease progression, especially regarding HFpEF. Hs-CRP has been associated with increased risk for cardiovascular disease in PREVEND.[14] However when adjusted for all CV variables, hs-CRP was not associated with a significantly increased riskfor either subtype of new onset heart failure.

Clinical consequences

Multiple intervention studies have clearly shown that patients with established HFrEF benefit from ACE-inhibitors, beta-blockers and mineralocorticoid receptor antagonists. But to date, not a single drug has proven to reduce mortality in patients with HFpEF nor is any drug recommended for the treatment of HFpEF in the current guidelines.[34] Our data clearly shows distinct clinical risk profiles for new onset HFpEF and HFrEF. This implies that prevention of new onset HFpEF might need a different approach as compared to prevention of HFrEF. Apart from treatment of hypertension, strategies to reduce an elevated UAE and prevention of permanent atrial fibrillation may help to prevent or delay new onset HFpEF. Future studies are needed to further evaluate effective preventive treatment for both different risk profiles.

Strengths and limitations

The large, community based cohort and long follow-up, standardized biomarker and clinical parameter measurements and the thorough validation of incident heart failure diagnosis, with little loss to follow-up, are strengths of our study. Our study is limited by the fact that the PREVEND study subjects are predominately Caucasian and our results can therefore not be extrapolated to subjects from other ethnicities. Also, heart failure was identified retrospectively by chart review. This could have resulted in underdetection of subjects with new onset

heart failure, especially HFpEF, when diagnosis is not pursued in the symptomatic patient with normal ejection fraction. Then, the PREVEND cohort was enriched for increased albumin excretion. Although we corrected for this by conducting a design-based analysis, we cannot exclude that our results are affected by the study design. However, compared to the Framingham cohort, UAE was not higher in PREVEND and incidence of all-cause mortality and new onset heart failure is comparable to unselected general population studies.[5, 22] Also, the multivariate cause-specific hazard model for HFrEF and HFpEF were adjusted for study design and are therefore not affected by the enrichment for higher albuminuria levels.

Conclusions

These data show incidence rates of both new onset HFpEF and HFrEF in a community-based cohort. Moreover, a differential clinical risk profile at baseline for both subtypes of HF was found. Apart from higher age and female gender, an increased urinary albumin excretion, atrial fibrillation and cystatin C emerged as new risk indicators for HFpEF. Overall, our data suggest that a differential approach is indicated in order to prevent both HFpEF and HFrEF.

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None of the authors have any potential conflict of interest to declare. There were no relevant financial activities outside the submitted work, or over the three years prior to submission. Also, there were no other relationships or activities that readers could perceive to have influenced, or that gave the appearance of potentially influencing what is written in the submitted work. FPB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All co-authors have contributed significantly to the manuscript, regarding interpretation of the data and revising it for important intellectual content.

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Conflict of interest

None declared.

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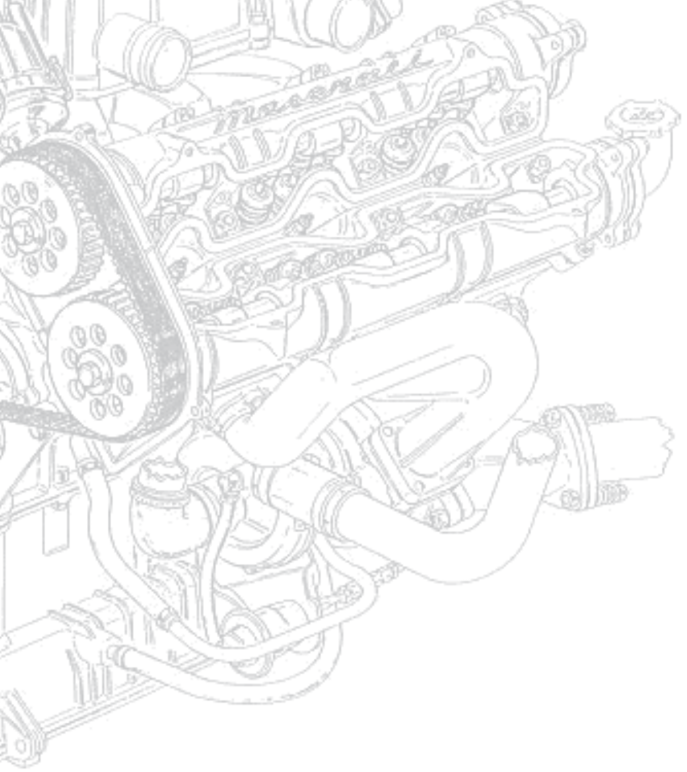

Chapter 3B

Heart failure with preserved and reduced ejection fraction: different risk profiles for different diseases

Barry A. Borlaug

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Approximately 15 million Europeans and 6 million Americans suffer from heart failure (HF), with annual direct and indirect costs in the billions.[1] About half of patients have a preserved ejection fraction (HFpEF), while the others display a reduced EF (HFrEF).[2,3] Clinical trials have unequivocally shown that treatments such as neurohormonal antagonists improve outcome in HFrEF, while similar trials in HFpEF have been neutral.[1,2] Several reasons have been proposed for this differential response, including unique pathophysiologies in HFpEF and HFrEF, differing degrees of neurohormonal activation, significant pathophysiological heterogeneity within the broad population of HFpEF patients, and higher non-cardiovascular mortality in HFpEF.[1,2] It is also possible that the heart in HFrEF displays greater plasticity and amenability to reverse remodelling, while changes in the mechanical properties of the heart and vasculature in HFpEF might be less reversible by the time symptoms develop. Thus, interventions designed to prevent HFpEF might be more effective to reduce the global disease burden. To better inform strategies to prevent HFpEF (and HFrEF), detailed insight is needed into disease-specific risk factors.

Brouwers and colleagues have now presented exciting new data identifying common and distinct risk profiles for incident HFpEF and HFrEF.[4] As part of the community-based Prevention of REnal and Vascular ENdstage Disease (PREVEND) study, 8,592 subjects living in Groningen, The Netherlands, underwent baseline medical examination along with blood testing and 24h urine sampling. After a median follow-up duration of 11.5 years, the authors undertook the ambitious enterprise of carefully reviewing all medical records to identify subjects developing incident HF. The HF diagnosis was established according to contemporary clinical, laboratory, and radiographic criteria as adjudicated by a panel of experienced cardiologists.[1] HFrEF was defined by EF ≤ 40% and HFpEF by EF ≥ 50%, meaning that the 'middle group' (EF 41– 49%) was excluded, though it is notable that only 1.3% of all HF subjects fell in this range. During the study period, 374 people developed HF (4.4%) of which 66% had HFrEF and 34% had HFpEF. The average time to diagnosis was 7.2 years, but intriguingly subjects with HFpEF were diagnosed ~2 years later than those with HFrEF. In multivariable analysis, incident HF was associated with older age, male sex, obesity, history of myocardial infarction, N-terminal pro brain nariuretic peptide (NT-proBNP) and highly-sensitive troponin T (hs-TnT).

These findings confirm previous studies examining risk factors for incident HF, but they say relatively little about the specific risk for the two HF phenotypes. To explore this question, the authors then performed causespecific hazard analyses to determine competing risk factors for HFrEF and HFpEF. In this analysis, female sex, atrial fibrillation (AF), increased urinary albumin excretion (UAE), and increased cystatin C (a marker of decreased renal function) emerged as being preferentially associated with risk of HFpEF rather than HFrEF (Figure 1). In contrast, typical coronary risk factors, such as male sex, smoking history, hs-TnT, and prior myocardial infarction were preferentially associated with risk of HFrEF. Age and NT-proBNP were associated with increased risk for both HF phenotypes, but intriguingly age was

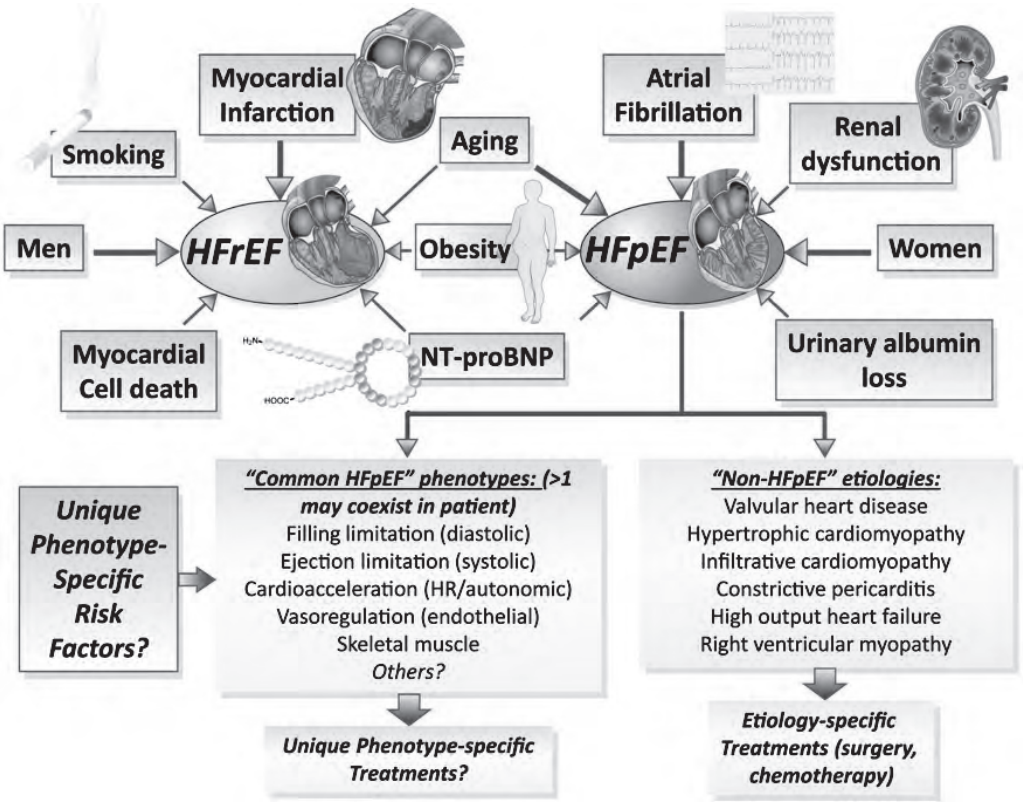

Figure 1 Top panels show risk factor profiles for incident HFrEF and HFpEF according to Brouwers et al.[4] Arrow widths are reflective of the magnitude of the associated hazard ratios. Bottom panels identify different sub-phenotypes within the broader category of HF with preserved EF. 'Non-HFpEF' aetiologies are separated based upon fundamental differences in pathophysiology, clinical course and treatment. 'Common HFpEF' phenotypes reflect pathophysiologic derangements noted in mechanistic studies where the 'non-HFpEF' aetiologies were excluded. These phenotypes are not mutually exclusive and several or all may coexist in a given patient.

a stronger risk factor for HFpEF, while NT-proBNP was a stronger risk factor for HFrEF. Obesity conferred similarly increased risk in both HF types. The authors conclude that these data provide further evidence in support of the notion that HFpEF and HFrEF are distinct HF phenotypes with separate pathophysiologies. These data confirm and extend upon recent studies examining risk factors for HFpEF and HFrEF preceding and at the time of diagnosis.[3,5–7] Strengths are the very high proportion of subjects with EF assessment (>98%), and the fact that HF was identified in both outpatients and hospitalized subjects. However, the retrospective assessment of HF status from chart review alone is a weakness.

For example, physical findings of congestion such as jugular distention or subjective complaints of exertional dyspnoea and fatigue are easy to miss in everyday practice, or may simply not have been documented in the clinical records. This HF underrecognition is more common in patients with preserved EF, where the diagnosis continues to be less seriously entertained than when the EF is grossly reduced.[2,8] Indeed, even when the patient with dyspnea is evaluated by a cardiologist, the diagnosis of HFpEF can be challenging to make, often requiring invasive assessment with or without provocative testing to render with confidence.[8] In PREVEND, HF was suspected in a large number of subjects where sufficient evidence was not felt to be present or alternative causes were observed (189, >50% of the HF group), and one wonders how many of these subjects might have been reclassified as HFpEF with more intensive evaluation. Presumably, the EF was normal in all of these subjects, since the presence of dyspnea in a patient with low EF will invariably lead to the diagnosis of HF. In addition to the potential underdetection of HFpEF in this retrospective assessment, the young mean age at entry (49 years) probably contributes to the lower prevalence of HFpEF relative to HFrEF. Indeed, community-based studies from the Framingham group have reported a mean age at diagnosis of 79 years in HFpEF.[5] Age was associated with increased risk for both HF phenotypes, but the impact was significantly greater for HFpEF. Thus, one would expect that as this population ages and is followed for a longer duration, HFpEF will ‘catch up’ in prevalence with HFrEF.

The findings of increased risk of incident HFpEF with female sex and AF are in keeping with previous studies.[3,5 – 7] While the mechanisms contributing to

greater risk of HFpEF in women remain incompletely understood, there appear to be important sexual dimorphisms in ventricular–vascular structure and function that develop with ageing which may predispose to HFpEF in women.[9] The presence of AF is another consistent factor that increases HFpEF risk. The impact of AF is even more apparent when considering that its prevalence at entry into PREVEND was similar in patients destined to develop HFpEF and HFrEF, yet AF conferred greater risk only in HFpEF (hazard ratio 3.8). These data are congruent with observations from the CHARM programme, where the presence of AF was associated with increased risk of HF hospitalization and death relatively more in HFpEF than in HFrEF.[10] It seems that the heart in patients with HFpEF (or at risk for HFpEF) is more reliant on atrial contraction to maintain haemodynamic compensation, and is thus more vulnerable to the deleterious effects of AF, leading to expression of the HF syndrome. These data support efforts to prevent the development of AF to help prevent HFpEF, in addition to diseases such as stroke.

Brouwers and colleagues also describe two previously unidentified risk factors for HFpEF, each of which is related to renal function: increased UAE and elevation in cystatin C. As with AF, baseline UAE and cystatin C levels were similar in subjects who ultimately developed HFpEF and HFrEF, meaning that greater burden of renal disease does not explain the association. Hypertension and diabetes were notably not predictive of HF risk, but each of these co-morbidities is in itself associated with renal dysfunction, albuminuria and AF, and this may explain the apparent lack of association. Loss of renal ability to dispose of excess volume would be expected to increase the risk of subclinical HF becoming manifest, and it appears that this vulnerability is greater in HFpEF. In line with this finding, ancillary data from the ALLHAT trial showed that the diuretic chlorthalidone reduced incident HFpEF compared with other antihypertensives.[11] In contrast, angiotensin-converting enzyme (ACE) inhibitors, which are well known to mitigate albuminuria, were not found to prevent HFpEF.

Brouwers and colleagues are to be congratulated for taking a major step forward in understanding the pathogenesis of HFpEF, but there is still much to learn. Within the broad category of ‘HFpEF’, there are several aetiologies that are currently defined separately in practice, and others that may require

further study for proper taxonomic classification (Figure 1). For example, patients with HF caused by severe mitral insufficiency or aortic stenosis will clearly behave differently and respond to treatments differently from patients with hypertrophic cardiomyopathy, constrictive pericarditis, or high output HF. However, despite this heterogeneity, these entities continue currently to be lumped together into the category of 'HFpEF'. As we move forward with epidemiological and physiological studies, these specific aetiologies of the HF syndrome should not be included under the broad term of HFpEF. Even when these 'non-HFpEF' causes are excluded, there are likely to be additional layers of pathophysiological heterogeneity in HFpEF that require better characterization. For example, we have recently shown that on average, cardiac output reserve predominantly limits exercise capacity in HFpEF,[12] and yet other groups have identified HFpEF patients with overly exuberant cardiac output responses,[13] or abnormalities peripheral to the heart in the skeletal muscle and vasculature that more potently dictate functional limitation. [14] Some HFpEF patients seem to express predominant diastolic limitations, yet most display numerous abnormalities in cardiovascular reserve, including diastolic dysfunction, systolic dysfunction, chronotropic incompetence, abnormal vasodilation, and endothelial dysfunction.[15] It seems likely that these different HFpEF subphenotypes might have their own unique risk factors and treatments. Future studies that more rigorously characterize the specific phenotypes within the broader population of HFpEF may hold the greatest promise finally to prevent and treat this deadly and growing disease for which there is no effective therapy.

Conflict of interest

None declared.

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Abstract

AIMS: We sought to identify and quantify the value of biomarkers for the incidence of new onset heart failure (HF) in a community-based cohort and in subgroups based on cardiovascular risk. In addition, we evaluated the prognostic value of all biomarkers for HF with reduced (HFrEF) and preserved ejection fraction (HFpEF) separately.

METHODS AND RESULTS: We related 13 biomarkers, reflecting diverse pathophysiologic domains to the incidence of new onset HF in 8,569 heart failure free participants of Prevention of REnal and Vascular ENdstage Disease (PREVEND; mean age: 49 years, 50% male). Subjects were categorized in two risk groups, based on the presence or absence of previous cardiovascular history. Per biomarker, we evaluated incremental value using Harrell's C coefficients. During a median follow-up of 12.5 years, 168 subjects (2.4%) were diagnosed with new onset HF in the low risk group (N = 6,915; Framingham Risk Score: 5.9%) and 206 (12.2%) subjects in the high risk group (N = 1,654; Framingham Risk Score: 18.6%). The risk association of natriuretic peptides, adrenomedullin, endothelin and galectin-3 with new onset HF was stronger in the high risk group (all $P<0.05$ compared to low risk group). For troponin-T, hs-CRP, urinary albumin excretion and cystatin C, there was equal risk association for new onset HF between both risk groups. The best model for new onset HF was achieved by the combination of NT-proBNP and hs-TnT, which significantly increased model accuracy by 9.0% to 0.81 ($P<0.001$) in subjects in the high risk group. Results for new onset HFrEF were similar to total HF. Except for a modest effect of cystatin C, no biomarker was associated with increased risk for HFpEF.

CONCLUSION: Risk stratification increases the incremental value per biomarker to predict new onset HF, especially HFrEF. However, we suggest that routine biomarker testing should be limited to the use of natriuretic peptides and troponin T in patients with increased cardiovascular risk. There was no clinically relevant association of biomarkers with new onset HFpEF, irrespective of risk stratification.

Chapter 4

Clinical risk stratification optimizes value of biomarkers to predict new onset heart failure in a community-based cohort

Frank P. Brouwers
Rudolf A. de Boer
Kevin Damman
Maarten P. van den Berg
Ron T. Gansevoort
Stephan J. Bakker
Hans L. Hillege
Dirk J. van Veldhuisen
Pim van der Harst
Wiek H. van Gilst

Submitted

Introduction

Heart failure (HF) is a progressive syndrome with high morbidity and one of the major causes of death in Western countries.[1-3] Since the discovery of natriuretic peptides, interest in using biomarkers alongside of clinical characteristics in order to guide early identification of subjects at risk has grown.[4] Several new biomarkers have emerged, but to date their clinical value remains under dispute. Proposed biomarkers include highly-sensitive troponin T (hs-TnT), urinary albumin excretion (UAE) or albumin to creatinine ratio, and highly-sensitive C-reactive protein (hs-CRP). The predictive value for new onset HF of novel biomarkers, like midregional proadrenomedullin (MR-proADM), galectin-3 or adiponectin, has not yet been well defined.[5-7] Previous multimarker studies showed little or absent incremental value of biomarkers, including natriuretic peptides, on top of conventional clinical characteristics for predicting new onset HF in the general population. Therefore, routine measurements are considered not cost-effective.[4,8,9] Identification of subgroups that might benefit from biomarker testing is suggested as a more effective strategy.[9] Another limiting factor is that most studies addressed HF in general, while we now acknowledge that HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) are distinct subtypes with different pathophysiology. Only few studies have evaluated biomarkers for HFrEF and HFpEF specifically, but all were underpowered to draw definitive conclusions and were based on prevalent cases of HF.[10,11]

A large panel of biomarkers is available in the present study population, representing a wide range of pathophysiological pathways for cardiovascular (CV) disease, i.e.: myocardial stress, myocyte injury, inflammation, renal dysfunction, extracellular matrix markers, renin angiotensin activation system, and other domains. We sought to identify and quantify the value of biomarkers for the prediction of new onset HF in a community-based cohort and in subgroups based on baseline CV risk. In addition, we evaluated the prognostic value of all biomarkers for HFrEF and HFpEF separately.

Methods

Study population

The study was performed using the data of the PREVEND (Prevention of

REnal and Vascular ENdstage Disease) cohort study, which has been described elsewhere.[12,13] In summary, from 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (N = 85,421) were asked to send in a first morning urine sample and complete a short questionnaire on demographics and CV disease history, and 40,856 subjects responded (47.8%). All subjects with UAE ≥10mg/l (N = 7,786) in their morning urine as well as a randomly selected control group with a UAE <10 mg/l (N = 3,395) were invited to an outpatient clinic for a detailed assessment of CV and renal risk factors, including filling out questionnaires, recording anthropometrics, and blood and urine sampling. After excluding subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects unable or unwilling to participate, a total of 8,592 subjects completed the screening programme. For the current analysis, we excluded subjects with known HF diagnosis at baseline (N = 23), leaving 8,569 eligble subjects.[14] The PREVEND study was approved by the institutional medical ethics committee and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Definitions

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits, measured using an automatic Dinamap XL Model 9300 series device. Hypertension was defined as systolic blood pressure >140mmHg, diastolic blood pressure >90mmHg, or self-reported use of antihypertensive medication. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2), and obesity was defined as a BMI>30kg/m^2. Hypercholesterolaemia was defined as total serum cholesterol >6.5 mmol/l (251 mg/dl) or a serum cholesterol >5.0 mmol/l (193 mg/dl) if a history of myocardial infarction (MI) was present or when lipid-lowering medication was used. Type 2 diabetes was defined as a fasting plasma glucose >7.0 mmol/l (126 mg/dl), a non-fasting plasma glucose >11.1 mmol/l, or use of anti-diabetic drugs. UAE was calculated as the average value from two consecutive 24h urine collections. The glomerular filtration rate (eGFR) was estimated using the simplified Modification of Diet in Renal Disease formula.[15] Smoking was defined as current smoking or smoking cessation within the previous year. History of MI of cerebrovascular accident (CVA) was defined as participant-reported hospitalization for at least 3 days as a result of this condition. Standard 12-lead electrocardiograms were recorded using the computer program Modular ECG Analysis System, and atrial

fibrillation (AF) was defined according to Minnesota codes 8.3.1 and 8.3.3.[16] Subjects were categorized in two risk groups, based on the presence or absence of previous CV history (referred to as "high risk" and "low risk", respectively). Previous CV history was defined as previous hospitalization for MI or CVA, or the use of anti-hypertensive, lipid-lowering or glucose-lowering drugs at baseline assessment. Anti-hypertensive drugs were defined as angiotension converting enzym inhibitors, angiotensin receptor blockers, diuretics or calcium antagonists. Lipid-lowering drugs were defined as any kind of statin. Glucose-lowering drugs were defined as oral anti-diabetic drugs. Information on medication use was obtained from the InterAction database (IADB), a community-based pharmacy database, contains detailed patient-specific drug prescription information on inhabitants of the city of Groningen and was linked to PREVEND data.[17] Prescription drugs were classified according to the Anatomical Therapeutic Chemical system. All PREVEND participants gave informed consent to link their data with pharmacy-dispensing data. The individual Framingham Risk Score was calculated according to D'Agostino et al.[18]

Assays

At baseline, EDTA plasma samples were drawn from all participants for biomarkerassessment. Aliquots of these samples stored immediately after collection at -80°C until analyses. Assays for all biomarkers in PREVEND have been described in detail elsewhere: N-terminal pro-B-type natriuretic peptide (NT-proBNP),[19] midregional pro-A-type natriuretic peptide (MR-proANP),[20] MR-proADM,[21] C-terminal-pro-Endothelin-1 (CT-proET-1),[22] galectin-3,[23] hs-TnT,[24] C-terminal pro-Arginine vasopressin (CT-proAVP), referred to as "copeptin",[25] procalcitonin,[26] hs-CRP,[27] cystatin C,[21] UAE,[28] renin,[29] and aldosterone.[29] For details on all assays, see supplementary material online.

New onset HF

Follow-up for the present investigation was defined as the time between the baseline visit to the outpatient department and the date of new onset HF up to January 1st, 2010. Subjects were censored at the date they moved to an unknown destination or at the last date of the follow-up, whatever date came first. Information on dates and causes of death for every participant was obtained from Statistics Netherlands[30] and coded according to the 10th revision of the International Classification of Diseases (ICD). Participants with a new diagnosis of HF were identified using criteria described in the HF Guidelines of the

European Society of Cardiology[31] and an endpoint adjudication committee ascertained the diagnosis of either HFrEF or HFpEF, as described elsewhere.[14] HF was classified as HFrEF or HFpEF based on left ventricular ejection fraction at the time of diagnosis. To prevent blending and dilution of epidemiological risk profiles between HFrEF and HFpEF, and to acknowledge the most recent trends in cut-off for HFrEF and HFpEF in accordance with the HF guidelines,[31] we have set the cut-off for HFpEF on ≥50% and the cut-off for HFrEF on ≤40%. Subjects in the grey area, with a LVEF 41-49% (N = 8), were excluded from the analyses to prevent blending and dilution of differential epidemiological profiles.

Statistical analysis

By design, subjects with an UAE ≥10 mg/l are overrepresented in the PREVEND. A design-based analysis was performed to overcome this overselection of subjects with elevated UAE. This statistical weighting method allows conclusions to be generalized to the general population.[21,32] Baseline continuous data are reported as mean (standard deviation) for normally distributed data. Because of skewed distribution, NT-proBNP, MR-proANP, galectin-3, hs-TnT, copeptin, procalcitonin, hs-CRP, UAE, cystatin C, renin en aldosterone were transformed to a 2-log scale and reported as median (inter-quartile range). This means that risk estimates should be interpreted as the relative risk if values were doubled (e.g. 1 to 2 mg/l or 10 to 20 mg/24h). To evaluate time to HF diagnosis for both risk groups, we performed Kaplan-Meier analyses (log-rank) using cumulative incidence. Two competing endpoints were distinguished: HFrEF and HFpEF. We fitted Cox-proportional hazards models to the data and adjusted our multivariate model for age, gender, BMI, smoking status, systolic blood pressure, AF, plasma glucose and total cholesterol levels, in accordance with previous results.[14] Schoenfeld residuals were calculated to assess whether proportionality assumptions were satisfied. We evaluted a P-value for interaction (P_{int}) between both risk groups, to compare the effects of biomarkers between both groups. To control for the type I error in the cause-specific hazard analysis (effect-by-covariate), a P_{int} between the high en low risk group of <0.10 is considered statistically significant.[14,33] To define the proportion of usable subject pairs in which outcome and prediction are concordant, we calculated the Harrell´s C coefficient for both models and the incremental value of biomarkers on this coefficient. Results are summarized as hazard ratios, with 95% confidence intervals based on robust standard error estimates. We accounted for multiple testing using Bonferroni correction: for each risk group,

Table 1 Baseline characteristics of subjects, divided by presence of CV history*

	Low risk N=6,915	High risk N=1,654	P-value
Heart failure (HFrEF / HFpEF-N)	168 (110 / 53)	206 (131 / 72)	
HF cases (HFrEF / HFpEF- %)	2.4 (1.6 / 0.7)	12.2 (7.9 / 4.4)	
Mean follow-up HF cases	8.6 (4.8-10.9)	7.3 (3.5-10.0)	0.002
HFrEF	7.8 (3.9-10.6)	6.1 (3.1-9.3)	
HFpEF	9.9 (7.5-11.3)	8.7 (5.4-10.8)	
Framingham Risk Score (%)	5.9 (2.5-14.7)	18.6 (9.0-32.3)	<0.001
Age (yrs)	47±12	59±11	<0.001
Males (%)	49.1	52.7	0.009
Caucasians (%)	95.5	95.7	0.795
BMI (kg/m^2)	26±4	28±4	<0.001
Waist circumference (cm)	87±13	95±13	<0.001
Systolic BP (mmHg)	126±19	140±22	<0.001
Diastolic BP (mmHg)	73±10	78±10	<0.001
Heart rate (bpm)	69±10	69±11	<0.001
Smoking or quit smoking <1yr (%)	39.6	31.5	<0.001
Selection criteria			
Previous myocardial infarction (%)	0.0	31.0	<0.001
Previous stroke (%)	0.0	5.0	<0.001
Anti-hypertensive medx	0.0	70.7	<0.001
Anti-cholesterol medx	0.0	20.7	<0.001
Anti-diabetes medx	0.0	7.0	<0.001
Biochemical markers			
Glucose (mmol/l)	4.8±1.0	5.4±1.7	<0.001
Cholesterol (mmol/l)	5.6±1.1	5.8±1.1	<0.001
HDL (mmol/l)	1.34±0.40	1.23±0.36	<0.001
LDL (mmol/l)	3.64±1.05	3.86±0.99	<0.001
Triglicerides (mmol/l)	1.11 (0.81-1.61)	1.40 (1.03-1.99)	<0.001
Serum Creatinine (umol/l)	82 (73-91)	86 (76-97)	<0.001
Serum Creatinine (mg/dl)	0.9 (0.8-1.0)	1.0 (0.9-1.1)	<0.001
eGFR (ml/min/1.73m^2)	82±14	75±16	<0.001
NT-proBNP (ng/l)	33 (15-62)	66 (30-150)	<0.001
MR-proANP (pmol/l)	45 (33-61)	62 (44-92)	<0.001
MR-proADM (nmol/l)	0.37±0.12	0.46±0.18	<0.001
CT-proET-1 (pmol/l)	33.8±13.6	39.4±17.1	<0.001
Galectin-3 (ng/ml)	10.6 (8.9-12.7)	12.2 (10.0-14.8)	<0.001
Hs-TnT (ng/l)	2.5 (2.5-4.0)	4.0 (2.5-8.0)	<0.001
Copeptin (pmol/l)	4.6 (2.9-7.4)	5.0 (3.0-8.5)	<0.001
Procalcitonin (ng/l)	1.5 (1.3-1.9)	1.8 (1.4-2.2)	<0.001
Hs-CRP (mg/l)	1.14 (0.50-2.69)	2.01 (0.93-4.31)	<0.001
Cystatin C (mg/l)	0.76 (0.68-0.85)	0.85 (0.74-0.98)	<0.001
UAE (mg/24h)	8.9 (6.2-15.3)	13.5 (7.3-34.0)	<0.001
Renin (mIU/ml)	17.8 (11.2-27.6)	19.3 (10.5-35.7)	<0.001
Aldosterone (pg/ml)	118 (93-154)	118 (93-154)	0.696

* Continuous variables are presented as mean+standard deviation and compared with the use of Student's t-test in case of normal distribution. In case of skewed distribution, continuous variables are presented as median (interquartile range) and compared using the Kruskall-Wallis test. Binary categorical variables were compared using standard Chi-squared tests. HFrEF denotes heart failure with reduced ejection fraction, HFpEF heart failure with preserved ejection fraction, BMI body-mass index, BP blood pressure blood pressure, HDL high density lipoprotein, LDL low density lipoprotein, eGFR estimated glomerular filtration rate, NT-proBNP N-terminal pro-B-type natriuretic peptide, MR-proANP midregional pro-A-type natriuretic peptide, MR-proADM midregional proadrenomedullin, CT-proET-1 c-terminal proendothelin-1, hs-TnT highly-sensitive troponin T, hs-CRP highly-sensitive C-reactive protein and UAE urinary albumin excretion

14 biomarkers were tested, and a P<0.004 (=0.05/13) was considered statistically significant. All statistical analyses were performed using StataIC (version 11.2 software for Windows). Figures displaying hazard ratios (HR) were made in SigmaPlot 10, by plotting estimated HR (calculated in StataIC).

Results

Baseline characteristics for both risk groups are presented in table 1. Subjects in the high risk group (N = 1,654, 19.3% of the total population) were older, more often male, had higher BMI, blood pressure and heart rate, and worse renal function compared to subjects in the low risk group (N = 6,915). Glucose, lipid parameters and all evaluated biomarkers were also higher at baseline for subjects in the high risk group (P<0.001), with the exception of aldosterone (P=0.696).

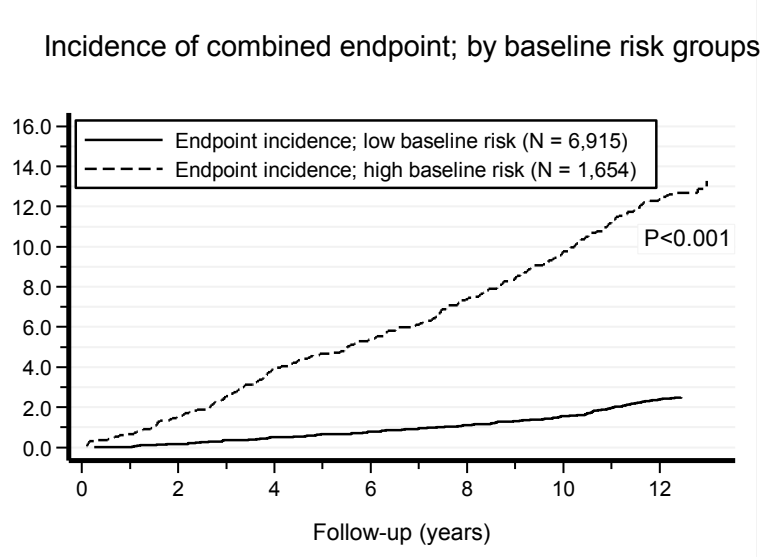


Figure 1 Cumulative incidence of new onset heart failure, divided by risk groups

Table 2 Relationship of single biomarkers with new onset heart failure in 8,569 subjects free of heart failure*

	Adjusted for age, sex		Multivariable adjusted**	
	HR (95% CI)	P-value	HR (95% CI)	P-value
NT-proBNP	2.11 (1.79-2.48)	<0.001	2.12 (1.76-2.55)	<0.001
MR-proANP	1.61 (1.32-1.98)	<0.001	1.62 (1.31-1.99)	<0.001
MR-proADM	1.26 (0.96-1.65)	0.096	1.10 (0.85-1.43)	0.457
CT-proET-1	0.98 (0.81-1.17)	0.791	0.96 (0.80-1.16)	0.703
Galectin-3	1.18 (1.03-1.36)	0.021	1.10 (0.95-1.28)	0.216
Hs-TnT	1.66 (1.49-1.85)	<0.001	1.56 (1.38-1.77)	<0.001
Copeptin	1.02 (0.84-1.23)	0.876	0.93 (0.75-1.14)	0.483
Procalcitonin	1.11 (0.98-1.25)	0.088	1.03 (0.88-1.20)	0.714
Hs-CRP	1.42 (1.17-1.71)	<0.001	1.27 (1.04-1.55)	0.022
Cystatin C	1.45 (1.24-1.69)	<0.001	1.39 (1.17-1.66)	<0.001
UAE	1.39 (1.26-1.53)	<0.001	1.23 (1.11-1.37)	<0.001
Renin	1.12 (0.94-1.33)	0.197	1.13 (0.95-1.35)	0.156
Aldosterone	1.04 (0.89-1.21)	0.656	1.00 (0.85-1.18)	0.990
ARR	0.91 (0.77-1.07)	0.263	0.88 (0.75-1.04)	0.143

* Hazard ratios for MR-proADM and CT-proET-1 are presented per increase of one standard deviation. Hazard ratios for all other biomarkers are presented per doubling of biomarker

** adjusted for age, sex, BMI > 30kg/m^2, smoking, systolic blood pressure, plasma glucose, total cholesterol. HR denotes hazard ratio, CI confidence interval, NT-proBNP N-terminal pro-B-type natriuretic peptide, MR-proANP midregional pro-A-type natriuretic peptide, MR-proADM midregional proadrenomedullin, CT-proET-1 c-terminal proendothelin-1, hs-TnT highly-sensitive troponin T, hs-CRP highly-sensitive C-reactive protein, UAE urinary albumin excretion, ARR aldosterone-renin ratio

The calculated median Framingham Risk Score was over three times higher in the high risk group (18.6% vs. 5.9%; P<0.001). During a median follow-up of 12.5 years (range 12.2-12.9; over 107,000 subjects years), 374 individuals were diagnosed with new onset HF, of whom 168 (2.4%) and 206 (12.2%) were in the low and high risk group, respectively. The median time to endpoint was 8.6 (range 4.8-10.9) years in the low risk group and 7.3 (range 3.5-10.0) years for the high risk group (P=0.002). Figure 1 shows the cumulative incidence of new onset HF, divided by risk group and adjusted for all-cause mortality.

New onset HF

Table 2 summarizes the results of the Cox-proportional hazard analysis for all biomarkers on new onset HF (unstratified for risk groups, nor for HFrEF and HFpEF). After adjustment for age and gender, NT-proBNP,

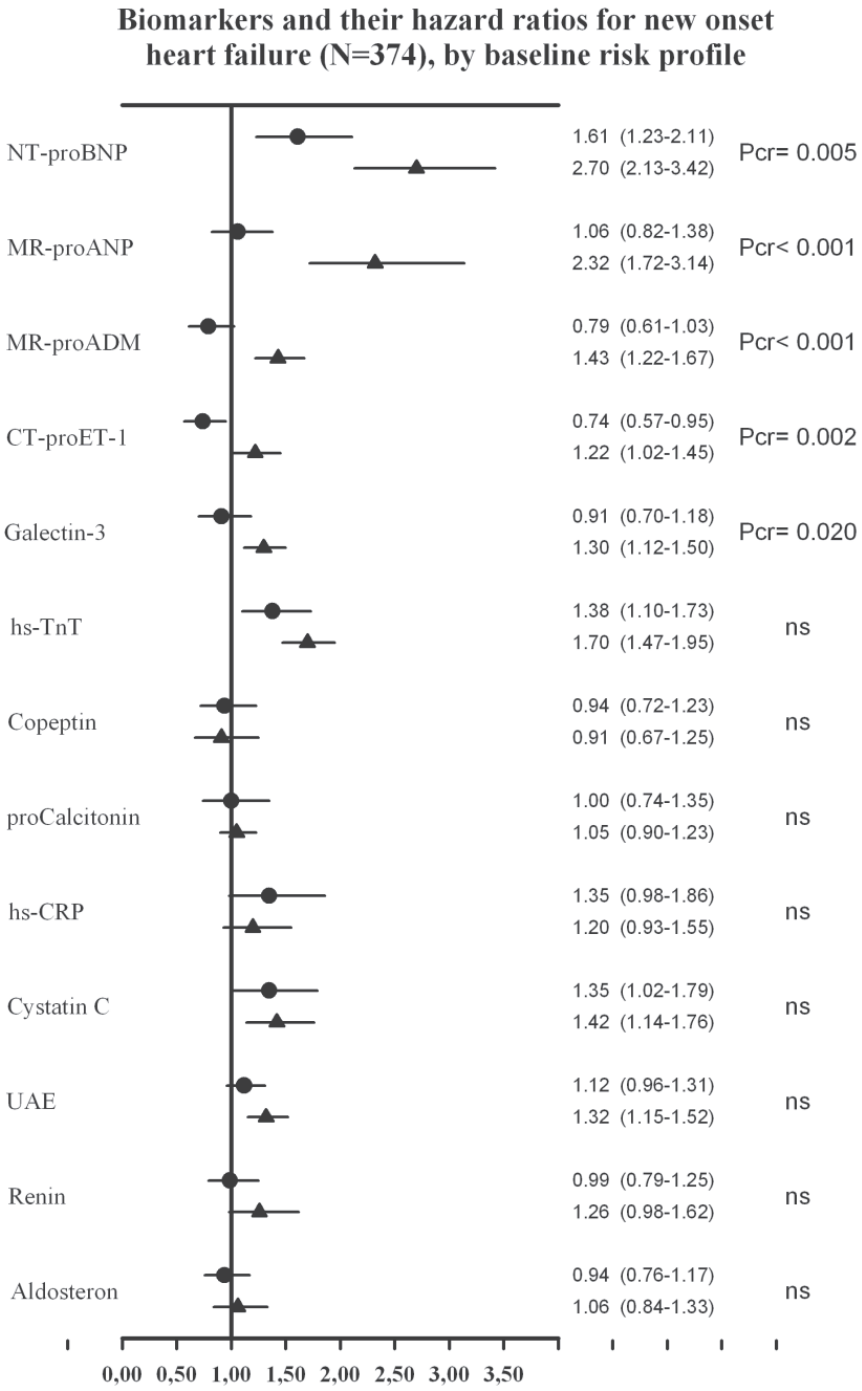


Figure 2 All biomarkers and their multi-adjusted relative risk for new onset heart failure, divided by risk groups. HF incidence in low risk and high risk group was 168 (2.4%) and 206 (12.2%), respectively.

Table 3 Harrell's C statistic of individual biomarkers with new onset heart failure

	Unstratified population		Subjects with low baseline risk (N=6,915)		Subjects with high baseline risk (N=1,654)	
	Harrell's C statistic Addition (%)	P-value	Harrell's C statistic Addition (%)	P-value	Harrell's C statistic Addition (%)	P-value
Age + sex*	0.826 (0.790-0.863)		0.787 (0.718-0.856)		0.743 (0.696-0.789)	
NT-proBNP	+ 4.7%	<0.001	+ 6.1%	0.007	+ 6.3%	0.006
MR-proANP	+ 2.2%	0.008			+ 5.2%	0.031
MR-proADM						
CT-proET-1						
Galectin-3					+ 1.3%	0.053
Hs-TnT	+ 2.5%	0.006			+ 5.7%	0.011
Copeptin						
Procalcitonin	+ 0.7%	0.058				
Hs-CRP	+ 1.9%	0.009	+ 4.3%	0.027		
Cystatin C	+ 1.0%	0.025				
UAE	+ 1.6%	<0.001	+ 2.0%	0.014	+ 2.2%	0.024
Renin						
Aldosterone						
ARR						

* no missing values for all biomarkers (N = 7,132)
CI denotes confidence interval, NT-proBNP N-terminal pro-B-type natriuretic peptide, MR-proANP midregional pro-A-type natriuretic peptide, MR-proADM midregional proadrenomedullin, CT-proET-1, c-terminal proendothelin-1, hs-TnT highly-sensitive troponin T, hs-CRP highly-sensitive C-reactive protein UAE urinary albumin excretion, ARR aldosterone renin ratio.

MR-proANP, hs-TnT, hs-CRP, cystatin C and UAE were significantly associated with increased risk for new onset HF. In multivariate analysis, the same biomarkers remained statistically significant. The proportionality assumptions for every biomarker in the model for total HF were satisfied (P>0.100). Hazard ratios for new onset HF, stratified for low and high risk, and their given interaction are depicted in Figure 2. After multivariable adjustment, higher NT-proBNP was associated with increased risk for new onset HF in both risk groups, although this association was significantly stronger for NT-proBNP in the high risk group (P_{int}=0.005). There was also an interaction present for the biomarkers MR-proANP, MR-proADM, CT-proET-1 and galectin-3 (all P_{int}<0.005; P_{int}<0.05 for galectin-3), indicating an increased risk for new onset HF specifically in subjects in the high risk category at baseline. Higher values of these biomarkers were not associated with risk for new onset HF in subjects in the low risk group. For hs-TnT, hs-CRP, UAE and cystatin C there was no interaction present, indicating that these markers are equally associated with outcome in both risk groups. Copeptin, procalcitonin, renin and aldosterone showed no association with increased risk for new onset HF.

The additional value of each biomarker to the model, compared to age and

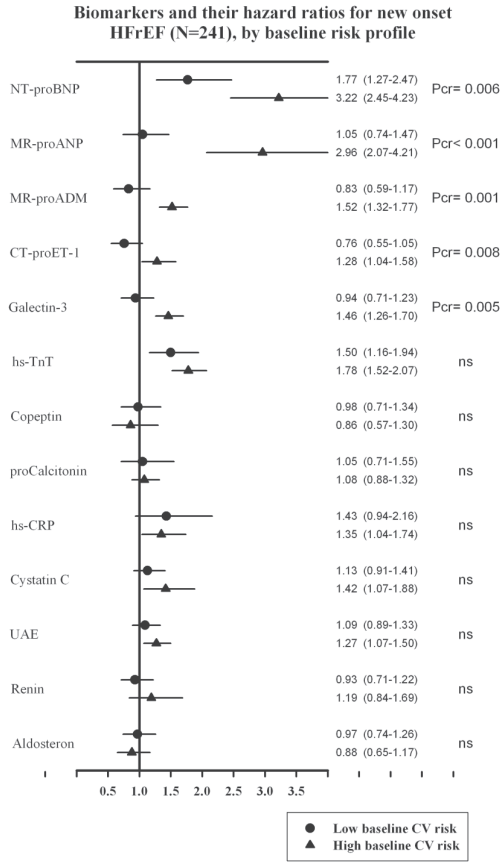


Figure 3A All biomarkers and their multi-adjusted relative risk for new onset HFrEF, divided by risk groups. HFrEF incidence in low risk and high risk group was 110 (1.6%) and 131 (7.9%), respectively.

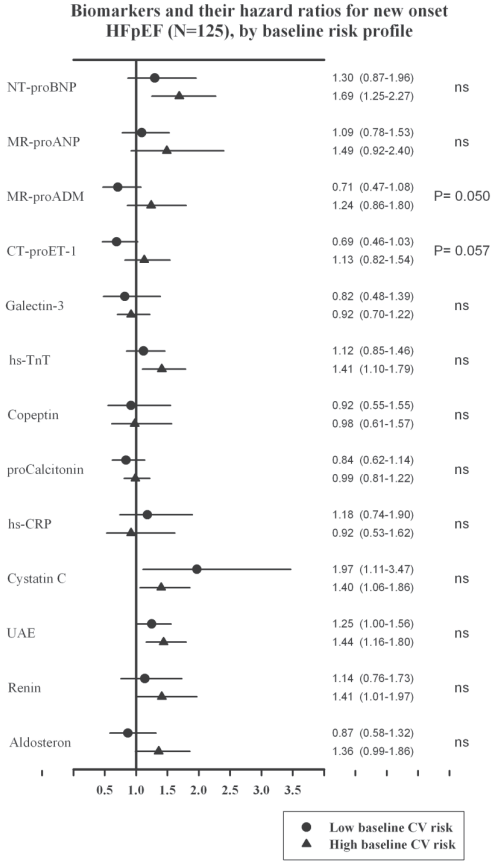


Figure 3B All biomarkers and their multi-adjusted relative risk for new onset HFpEF, divided by risk groups. HFpEF incidence in low risk and high risk group was 53 (0.8%) and 72 (4.4%), respectively.

gender alone, was subsequently calculated and summarized in Table 3. For the low risk group, NT-proBNP, hs-CRP and UAE modestly improved model fit by 6.1, 4.3 and 2.0%, respectively; other biomarkers did not improve the model. The model for subjects with high baseline risk improved with the addition of NT-proBNP, hs-TnT, MR-proANP, UAE and galectin-3, in order of incremental value.

During the follow-up period, there were 169 myocardial infarctions, which was followed by new onset HF in 43 (25.4%) subjects (N = 26 in the low risk group; N = 17 in the high risk group, see Supplementary Table S2). A sub-analysis was performed without these 43 subjects, to account for possible bias in the risk association for all separate biomarkers with myocardial infarction, instead of new onset heart failure, HFrEF or HFpEF. This did not change the results.

HFrEF vs. HFpEF

Hazard ratios for all biomarkers in both risk groups and their potential interaction are presented in Figure 3A (HFrEF) and Figure 3B (HFpEF). Results for new onset HFrEF were comparable to total new onset HF, where the same biomarkers were associated with increased risk for HFrEF in subjects with high baseline CV risk. For new onset HFpEF, there was an interaction present between risk groups for MR-proADM and CT-proET-1. However, the associated risk for HFpEF itself was not significant in both risk groups separately. Renal function, represented by cystatin C, was associated with new onset HFpEF, with comparable hazard ratios for both risk groups at baseline. The proportionality assumptions for every biomarker in the models for HFrEF and HFpEF were satisfied (P>0.100).

Model performance

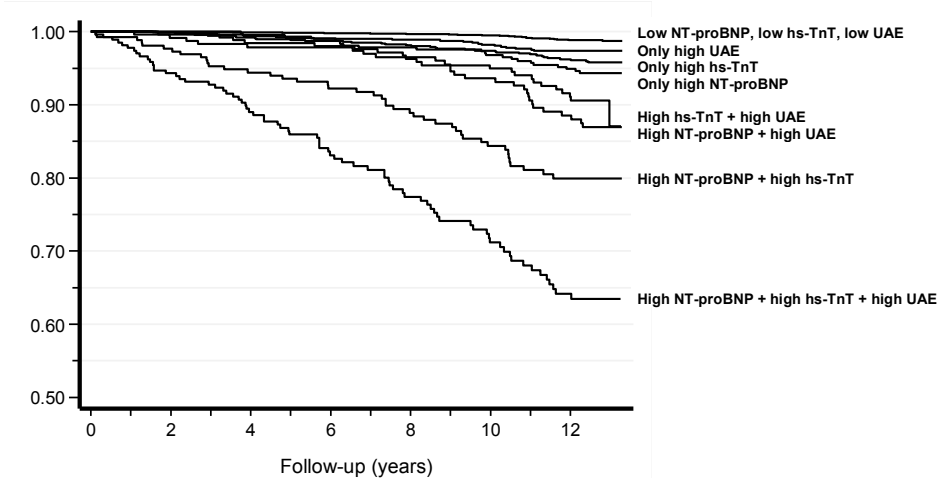
The model with best performance for the prediction of new onset HF in the entire cohort was achieved by the combination of NT-proBNP, hs-TnT and UAE, which significantly increased model accuracy by 5.6% to 0.87 (P<0.001). These biomarkers were subsequently assessed in a multimarker score and dichotomized according to 75th percentile. Table 4 shows the univariate and multivariate hazard ratios (for total new onset HF) for the different combinations of the high and low values of these three biomarkers. All three entities alone were not associated with an increased risk for total new onset HF, whereas the combination of any two entities increased the risk substantially. Figure 4 shows the Cox-regression survival curves for different combination of biomarkers. When high levels of NT-proBNP, hs-TnT and UAE were all present, the adjusted

Table 4 Combination of biomarkers and outcome

			Univariate		Multivariate	
	N*	HF	HR	P-value	HR	P-value
Low NT-proBNP, hs-TnT and UAE	3860	41	1.00		1.00	
Only high UAE	845	20	1.67 (0.91-3.05)	0.097	0.97 (0.51-1.87)	0.936
Only high hs-TnT	462	22	4.80 (2.39-9.61)	<0.001	1.94 (0.88-4.23)	0.098
Only high NT-proBNP	922	34	3.47 (1.90-6.33)	<0.001	2.17 (0.96-4.92)	0.062
High hs-TnT + high UAE	262	27	8.56 (4.13-17.72)	<0.001	2.32 (1.23-4.38)	0.009
High NT-proBNP + high UAE	245	22	10.69 (5.38-21.21)	<0.001	4.87 (2.21-10.75)	<0.001
High NT-proBNP + high hs-TnT	262	43	22.01 (12.56-38.51)	<0.001	5.54 (2.75-11.16)	<0.001
High NT-proBNP + high hs-TnT + high UAE	274	75	43.52 (26.20-72.31)	<0.001	7.28 (3.66-14.49)	<0.001

* no missing values for all biomarkers (N = 7,132)

HF denotes heart failure, HR hazard ratio, NT-proBNP NT-proBNP N-terminal pro-B-type natriuretic peptide, hs-TnT highly-sensitive troponin T, UAE urinary albumin excretion. Low NT-proBNP ≤73.5ng/l, high NT-proBNP >73.5ng/l; low hs-TnT ≤5ng/l, high hs-TnT >5ng/l; low UAE ≤17.7mg/24h, high UAE >17.7mg/24h



3860	3775	3665	3553	3461	3357	3201	Low NT-proBNP, low hs-TnT, low UAE
845	824	804	780	749	722	672	Only high UAE
462	448	430	404	387	370	344	Only high hs-TnT
922	903	862	835	804	766	720	Only high NT-proBNP
262	256	244	236	221	206	181	High hs-TnT + high UAE
245	235	222	213	205	190	169	High NT-proBNP + high UAE
262	246	225	204	183	162	140	High NT-proBNP + high hs-TnT
274	242	209	172	144	119	94	High NT-proBNP + high hs-TnT + high UAE

Figure 4 Survival function for new onset heart failure stratified by different combinations or biomarkers. Low NT-proBNP ≤73.5ng/l, high NT-proBNP >73.5ng/l; low hs-TnT ≤5ng/l, high hs-TnT >5ng/l; low UAE ≤17.7mg/24h, high UAE >17.7mg/24h. NT-proBNP denotes N-terminal pro-B-type natriuretic peptide, hs-TnT highly-sensitive troponin T, UAE urinary albumin excretion.

hazard ratio was strongly increased: 7.28; 95% CI 3.66-14.49; P<0.001 for total new onset HF.

Discussion

In the present study, we report that an array of biomarkers has limited value in predicting new onset HF in a large middle-aged cohort from the general population. However, the predictive value for new onset HF of several CV biomarkers substantially increased when a high baseline risk group was separately studied. In subjects with low CV risk, apart from the established biomarkers NT-proBNP and hs-TnT, no CV biomarkers were associated with new onset HFrEF. Finally, regardless of baseline risk group, no biomarkers were associated with new onset HFpEF, except for cystatin C, which showed a modest association. Dividing subjects from the general population based on previous history of CV disease, appears a useful tool to differentiate high risk from low risk individuals.

Early detection of increased risk for diagnosis of a high mortality condition such as HFrEF and HFpEF could alert physicians and prompt preventive measures and treatment early in the disease process, and may be helpful in attenuating disease progression.

At least two large studies have performed multi-biomarker analyses for new onset HF. Velagaleti et al. identified NT-proBNP and albumin-to-creatinine ratio to be associated with new onset HF.[8] Smith et al. associated natriuretic peptides with improved risk classification for HF in addition to conventional risk factors.[9] Galectin-3 was recently shown to be associated with increased risk for new onset HF, on top of conventional risk factors and BNP in the community.[6] Similar to our analyses, these studies provide data from large community-based populations with long-term follow-up and show comparable incidence rates of new onset HF. However, both previous studies also showed that CV biomarkers have little or absent incremental value, on top of clinical characteristics, with or without the combination with NT-proBNP to predict new onset HF. This may be explained by the diversity of subjects at baseline (i.e. ethnicity, CV risk) and lack of power due to a low number of new onset HF cases. But probably more important, there is increasing evidence of substantial epidemiologic differences between subjects with new onset HFrEF and HFpEF long before time of diagnosis, and these phenotypes should be clearly distinguished.[14,34] Our analysis adds several novel aspects. To increase the incremental value of several biomarkers, we divided our cohort using a combination of common clinical risk stratification of subjects and performed separate analyses for HFrEF vs. HFpEF. We also assessed biomarkers from multiple domains, reflecting different pathological processes that are operative in HF.[35]

Clinical risk stratification: High vs. low risk at baseline

Using a simple clinical stratification, we incurred large differences in baseline CV risk (confirmed by the Framingham risk score), a substantial shorter follow-up time to incident HF events and an increased incidence of new onset HF. We confirm the predictive ability of NT-proBNP for new onset HF, and show increased ability of this biomarker for subjects with high baseline risk, compared to subjects with low baseline risk. We also confirm the association between higher circulating galectin-3 concentrations and the increased risk for new onset HF in the general population.[6,23] However, this

appears only significant in subjects with high CV risk. Similar results were obtained with novel CV biomarkers like MR-proANP, MR-proADM and CT-proET-1, which were only modestly associated with increased risk for developing HF in subjects with high baseline risk. Increased levels of hs-TnT, hs-CRP, cystatin C and UAE have been associated with worse prognosis in prevalent HF,[36-39] but did not show differences in hazard ratios between both risk groups. In subjects with low CV risk at baseline, no novel CV biomarkers were associated with new onset HF.

No prospective data have been reported describing the predictive role of ANP for new onset HF to date, although it has been shown that increased ANP independently predicts left ventricular hypertrophy in a general population and outcome in chronic HF patients.[40,41] Natriuretic peptides showed the strongest prognostic value for new onset HF, specifically in subjects with high baseline CV risk. However, the prognostic value of these peptides is not independent of each other. MR-proADM and CT-proET-1, both involved in the homeostasis of the sodium and water balance, have shown promising results in predicting outcome in chronic HF patients,[42,43] however their incremental value in predicting CV outcome is still under debate.[9,44] This might be explained by the fact that both MR-proADM and CT-proET-1 are typically increased in those at risk for CV disease, such as elderly subjects, with or without chronic kidney disease, albuminuria or type 2 diabetes.[21,42,45,46] Through stratification of baseline CV risk, we were able to improve the ability of these biomarkers to predict new onset HF.

HFrEF vs. HFpEF

The modest incremental value of biomarkers in previous studies might be partly explained by lack of differentiation between HFrEF and HFpEF, which are known to represent different epidemiologic profiles, even years before diagnosis, and could therefore be considered different diseases.[14,34] Our data support this notion, but also give new information on the ability of biomarkers to predict either HFrEF or HFpEF. Biomarkers were able to identify subjects at risk for HFrEF, but not HFpEF. This confirms that these phenotypes can not only be regarded as different disease states, but also that HFpEF patients are much harder to identify up front. Whether this is caused by specific underlying pathophysiology, the severity of the disease at initial diagnosis, or even the diagnosis itself, should be the focus of future research.

Clinical implications

Compared to previous large biomarker studies, we have also associated several biomarkers with new onset HF. However, we must also emphasize the modest predictive value of all evaluated biomarkers in this community-based cohort. By baseline risk stratification, several CV biomarkers increased the discriminatory power of the statistical model in the high risk group, in contrast with to the low risk group, where there was overall very modest incremental value of all evaluated biomarkers. Out of all possible combinations, the greatest improvement in model fit for high risk subjects was accomplished with both NT-proBNP and hs-TnT. Screening tactics for the general population, or beneficial effects of invididual risk stratification into low of high risk groups needs to be evaluated in future studies, especially for HFpEF. However, from the perspective of cost-effectiveness, we propose to refrain from measuring biomarkers in subjects with low baseline CV risk. Future studies are needed to evaluate the incremental value of other biomarkers, especially for HFpEF.

Strengths and limitations

The large PREVEND cohort, with over 107,000 patient years of follow-up and thoroughly validated cases of new onset HF, provides good opportunity for large-scale evaluation of biomarkers. We offer a broad range of biomarkers, reflecting multiple domains associated with HF development. In addition, we have identified new onset HFrEF next to HFpEF, giving insight into pathophysiologic pathways for both HF phenotypes. Our study is limited by the fact that the PREVEND study subjects are predominately Caucasian, so our results cannot be extrapolated to subjects of other ethnicity. Serial biomarker data are also not available. Furthermore, we aimed to study differential risk association for HF (and specifically for HFrEF and HFpEF) between low and high risk groups, and did therefore not include mortality as an additional competing risk state in the current analysis. Finally, the PREVEND cohort was enriched for increased albumin excretion. We therefore conducted design-based analyses, making our results valid for the general population.

Conclusions

In this community-based cohort, several biomarkers were associated with new onset HF. Risk stratification further increases the incremental value per biomarker to predict HF, especially HFrEF. However, we conclude from our data that routine biomarker testing should be limited to the use of NT-proBNP and hs-TnT in patients with an increased CV risk. There was no clinically relevant association of any biomarker with new onset HFpEF, irrespective of risk group.

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Conflict of interest statement

There were no relevant financial activities outside the submitted work. FPB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All co-authors have contributed significantly to the manuscript, regarding interpretation of the data and revising it for important intellectual content.

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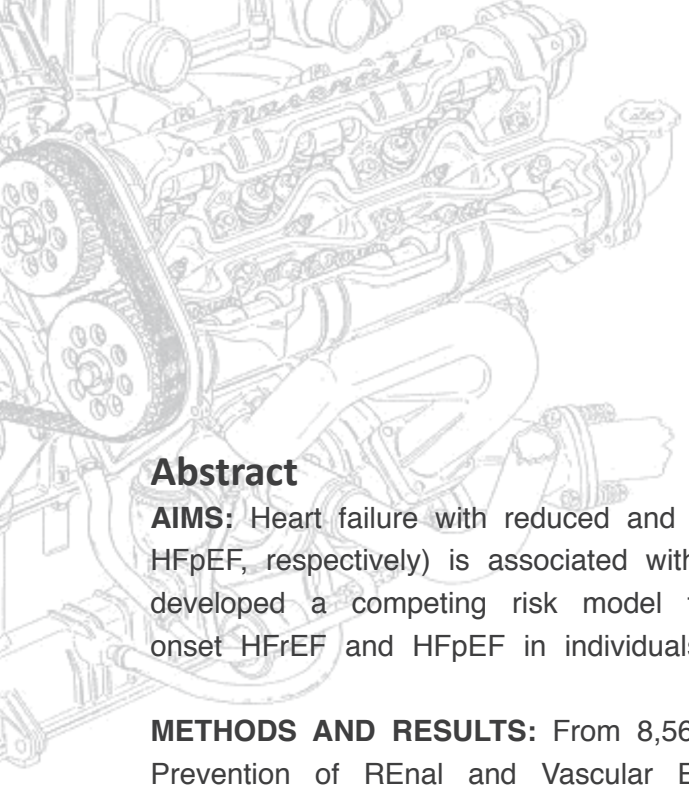

Abstract

AIMS: Heart failure with reduced and preserved ejection fraction (HFrEF, HFpEF, respectively) is associated with high mortality and morbidity. We developed a competing risk model for simultaneously predicting new onset HFrEF and HFpEF in individuals from a community-based cohort.

METHODS AND RESULTS: From 8,569 heart failure-free subjects of the Prevention of REnal and Vascular ENdstage Disease (PREVEND), a community-based, middle-aged cohort study, we identified 374 subjects with new onset heart failure, of whom 241 (66%) had HFrEF, according to the guidelines of the European Society of Cardiology. Weibull regression models were used with a subject's age as the time scale to describe the cause-specific hazard functions of the state transitions included in our model. The model's accuracy in predicting the 10-year cumulative incidences of new onset HFpEF and HFrEF was internally validated considering calibration and discrimination. 21 easily available risk factors in daily clinical practice comprised the PREVEND risk model. The mean observed vs. predicted 10-year cumulative incidence was 2.1% and 2.3% for HFrEF and 1.0% and 1.1% for HFpEF. Predictors for new onset HFpEF were cystatin C, UAE and systolic blood pressure. Specific predictors for HFrEF were smoking, hs-Troponin T, male gender and cholesterol. NT-proBNP and myocardial infarction predicted both outcomes, however stronger for HFrEF. BMI also predicted both outcomes, but stronger for HFpEF. The corresponding values of the c statistic were 0.70 for HFrEF and 0.60 for HFpEF.

CONCLUSION: We present the first available risk prediction model for early identification of subjects at risk for new onset HFrEF and HFpEF. Even in a well-defined community-based cohort with extensive follow-up, the prediction of new onset heart failure, in particular HFpEF, remains challenging.

Chapter 5

The PREVEND risk model for new onset heart failure with preserved and reduced ejection fraction

Frank P. Brouwers
Qi Cao
Douwe Postmus
Peter P. van Geel
Adriaan A. Voors
Ron T. Gansevoort
Rudolf A. de Boer
Pim van der Harst
Dirk J. van Veldhuisen
Wiek H. van Gilst
Hans L. Hillege

Submitted

Introduction

Heart failure is a progressive syndrome with a high morbidity and is one of the major causes of death in Western countries.[1-3] Variable mortality rates have been reported, accounting for the severity of the underlying disease and various other factors. For example, in most surveys, patients with HFpEF have a better survival compared with patients with HFrEF.[4, 5] Multiple successful clinical trials showed substantially improved prognosis for patients diagnosed with HFrEF,[6] whereas no randomized clinical trial yet decreased mortality rates for subjects with HFpEF.[7] Most recent studies on new onset heart failure have shown clear distinctive clinical patterns between the two types of heart failure.[8, 9] Since the difference in patient profiles, clinical outcomes and differential benefits of drug treatment, HFrEF and HFpEF should be considered separately when analyzing the risk of new onset heart failure. However, a risk prediction model that discriminates between subjects at risk for HFpEF and HFrEF has not yet been developed.

Recently, we identified all cases of new onset heart failure during 12.5 years of follow-up in a community-based cohort and adjudicated them as either HFrEF or HFpEF.[8] In the current investigation, we developed a risk prediction model for both types of new onset heart failure, using regular and easily available clinical and biochemical measurements.

Methods

Study population

The study was performed using the data of the PREVEND (Prevention of REnal and Vascular ENdstage Disease) cohort study, which has been described elsewhere.[10, 11] In summary, from 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (N = 85,421) were asked to send in a first morning urine sample and complete a short questionnaire on demographics and cardiovascular disease history, and 40,856 subjects responded (47.8%). All subjects with a urinary albumin excretion (UAE) ≥10mg/l (N = 7,786) in their morning urine as well as a randomly selected control group with a UAE <10 mg/l (N = 3,395) were invited to an outpatient clinic for a detailled assessment of cardiovascular and renal risk factors, including filling in questionnaires, recording anthropometrics, and blood and urine sampling. After excluding subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects unable or unwilling to participate, a total of 8,592 subjects completed the screening programme. Within these subjects, 23 (0.3%)

had a diagnosis of heart failure before the start of PREVEND.[8] These patients were excluded from the present analysis. Thus in total, 8,569 heart failure-free subjects comprised the present study population. The PREVEND study was approved by the institutional medical ethics committee and conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent.

Definitions

Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of the two visits, measured using an automatic Dinamap XL Model 9300 series device. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). UAE was calculated as the average value from two consecutive 24h urine collections. Smoking was defined as current nicotine use or smoking cessation within the previous year. History of myocardial infarction was defined as participant-reported hospitalization for at least three days as a result of this condition. Standard 12-lead electrocardiograms were recorded using the computer program Modular ECG Analysis System, and atrial fibrillation (AF) was defined according to Minnesota codes 8.3.1 and 8.3.3.[12]

Assays

At baseline, EDTA plasma samples were drawn from all participants for biomarker assessment. Aliquots of these samples were stored immediately after collection at -80°C until analyses. N-terminal pro-B-type natriuretic peptide (NT-proBNP) and highly-sensitive C-reactive protein (hs-CRP) were measured, as described in detail elsewhere.[13, 14] Highly-sensitive troponin T (hs-TnT) was measured using Modular Analytics serum work areas, with <10% coefficient of variation at the 99th percentile of the reference range (Roche Diagnostics).[15] Urinary albumin concentration was determined by nepholometry, with a threshold of 2.3 mg/l and intra- and interassay coefficients variation of 2.2 and 2.6%, respectively (BNII, Dade Behring Diagnostica, Marburg, Germany).[10]

Heart failure and cardiovascular events

As described before, follow-up for the present investigation was defined as time between the baseline visit to the outpatient department and the date of new onset heart failure, death or 01 January 2011.[8] Subjects were censored at the date they moved to an unknown destination or at the last date of follow-up (01 January 2011), whichever date came first. Information on dates and

causes of death for every participant were obtained from Statistics Netherlands,[16] and coded according to the 10th revision of the International Classification of Diseases (ICD). Participants with a new diagnosis of heart failure were identified using criteria described in the Heart Failure Guidelines of the European Society of Cardiology,[6] and an endpoint adjudication committee ascertained the diagnosis of either HFrEF or HFpEF, as described elsewhere.[8] Based on left ventricular ejection fraction (LVEF) at the time of diagnosis, heart failure was classified as HFrEF or HFpEF (LVEF ≤40% or ≥50%, respectively).

Model structure

To predict the 10-year cumulative incidences of new onset HFpEF and HFrEF, we fitted a competing risk model to the observed outcomes in the study population.[17] The model consisted of one starting state (free of heart failure) and three absorbing states reflecting the occurrence of three competing causes of failure: new onset HFpEF, new onset HFrEF, and death before the onset of heart failure (see Figure 1 for a schematic representation). The death state included eight subjects who developed new onset heart failure with a LVEF between 41% and 49% at the time of diagnosis, as these subjects are also no longer at risk for developing either new onset HFpEF or new onset HFrEF. The cause-specific hazard functions were assumed to have a proportional hazard structure with a Weibull baseline hazard function and a subject's age as the time scale.[18] To account for the overrepresentation of subjects with an elevated UAE (≥10 mg/l) in our study population, subjects were stratified into normal or elevated UAE and separate baseline hazard functions were fitted to each stratum. The effects of the explanatory covariates on the baseline hazard functions were assumed to be the same in each stratum. A detailed description of the model's regression equations and how these equations were combined to obtain absolute risk predictions is provided in Appendix I.

Parameter estimation

To fit the cause-specific hazard functions to the observed outcomes in the PREVEND study population, the following procedure was followed. First, a set of routinely available candidate predictor variables (Appendix II) was established to build up the initial full models. Subsequently, model building was performed by applying a backward selection procedure with a nominal significance level of 10% for variable exclusion. As missing values were

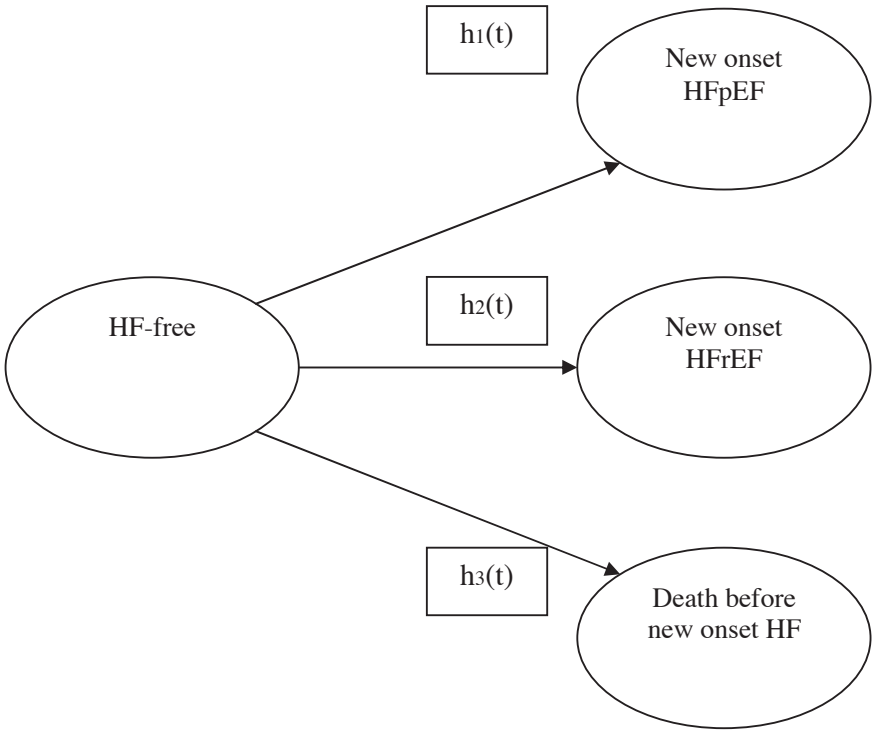

Figure 1 Schematic representation of the competing risk model structure

present in several of the candidate predictor variables, multiple imputation was performed to obtain five imputed data sets. Rubin's rules were used to obtain pooled estimates of the regression coefficients and their standard errors.[19, 20] As age is used as the time scale of the cause-specific hazard functions, it is unnecessary to use it as a covariate in the regression equations. Age was therefore not included in the list of candidate predictor variables. In addition, as subjects were not observed from birth but rather from their time of entry into the study, the use of age as the time scale causes the data to be left-truncated. This delayed entry into the risk set was accounted for when estimating the regression coefficients of the cause-specific hazard functions. Most variables entered the models as linear terms, except for triglycerides, creatinine, UAE, hs-CRP, and NT-proBNP, for which the log transformation was applied. For hs-TnT, the lower detection limit of 2.5 ng/l was reached for 57.5% of the subjects. This variable was therefore entered in the model by including the following two terms: a dummy variable indicating whether a subject's hs-TnT value fell below the detection limit, and a continuous variable taking on the value log(hs-TnT –2.5) for subjects with an hs-TnT value above the detection limit and 0 otherwise.

Model validation

The model's accuracy in predicting the 10-year cumulative incidences of new onset HFpEF and HFrEF was internally validated by considering calibration and discrimination. Calibration was assessed graphically by plotting for each decile of predicted 10-year cumulative incidence the mean predicted 10-year cumulative incidence against the observed 10-year cumulative incidence within this same decile. To account for competing risk, the observed 10-year cumulative incidences were estimated by the empirical cumulative incidence estimator.[17] Discrimination was assessed by calculating Harrell's C discrimination index,[21] using Wolbers et al. adapted definition of the risk set to account for the occurrence of competing events that preclude the occurrence of the event of interest.[22]

Results

Patient characteristics

During a median follow-up of 12.5 years (IQR: 12.2~12.9), 366 individuals (4.3%) were diagnosed with new onset HFpEF or HFrEF. Out of these patients, 125 (34.2%) were classified as HFpEF and 241 (65.8%) as HFrEF. Eight individuals (0.1%) were diagnosed with new onset heart failure with a LVEF between 41% and 49%. 710 individuals (8.3%) died before the onset of heart failure. The average time to diagnosis of new onset heart failure was 7.8 (IQR 3.9~10.5) years (6.6 (3.5~10.0) years for HFrEF and 9.2 (6.4~11.0) years for HFpEF).

Baseline characteristics of subjects experiencing an event are depicted against event-free subjects in Table 1. Compared to subjects with new onset HFpEF, levels of creatinine, hs-TnT, and NT-proBNP were higher for subjects with new onset HFrEF. The proportions of males and smokers were also larger for subjects with new onset HFrEF compared to subjects with new onset HFpEF.

Predictors for HFrEF and HFpEF

The beta coefficients and corresponding hazard ratios for the final models of the cause-specific hazard functions are listed in Table 2. Specific risk factors for new onset HFpEF were cystatin C, UAE and systolic blood pressure. Specific predictors for new onset HFrEF were smoking, hs-TnT and total cholesterol. Increased levels of NT-proBNP and a previous history of myocardial infarction were both predictors for HFrEF and HFpEF, although more for HFrEF. The same applies to an increased BMI, which was more predictive for HFpEF

Table 1 Baseline characteristics of the PREVEND study population, divided by heart failure and death during follow-up*

	No HF / death N = 7,485	HFpEF N = 125	HFrEF N = 241	Death before HF N = 718
Demography				
Age (yrs)	47±12	63±9	62±10	63±10
Males (%) #	47.4	48.0	73.4	67.3
BMI (kg/m^2)	26±4	29±5	28±4	27±4
Smoking or quit <1 year (%) #	37.4	28.8	43.5	44.1
Systolic BP (mmHg)	127±19	149±25	145±22	142±23
Diastolic BP (mmHg)	73±10	79±9	80±10	79±10
Heart rate (bpm)	69±10	70±12	70±12	71±12
Baseline Medical history				
Myocardial infarction (%)	4.1	19.5	28.8	16.1
Stroke (%)	0.6	3.3	3.0	3.2
Atrial fibrillation (%)	0.8	5.0	4.6	2.8
Laboratory values				
Glucose (mmol/l	4.8±1.0	5.6±2.1	5.4±1.7	5.4±1.9
Cholesterol (mmol/l)	5.6±1.1	6.0±1.0	6.0±1.0	6.0±1.2
HDL (mmol/l)	1.33±0.40	1.27±0.35	1.20±0.36	1.23±0.39
LDL (mmol/l)	3.63±1.04	4.03±0.98	4.05±0.98	4.01±1.06
Triglycerides (mmol/l)	1.14 (0.83-1.66)	1.36 (1.02-1.78)	1.41 (0.97-2.03)	1.33 (0.97-1.92)
Cystatin C (mg/dl)	0.78±0.18	0.92±0.26	0.93±0.21	0.94±0.38
Serum Creatinine (umol/l) #	82 (73-91)	81 (72-96)	90 (80-102)	87 (76-99)
UAE (mg/24h)	8.9 (6.2-15.5)	20.4 (9.9-57.8)	19.2 (9.3-50.8)	16.3 (8.7-46.1)
Hs-CRP (mg/l)	1.16 (0.52-2.74)	2.05 (0.88-4.45)	2.48 (1.24-4.85)	2.29 (1.10-4.97)
NT-proBNP (ng/l) #	34 (15-65)	86 (37-167)	121 (45-355)	72 (32-157)
Hs-TnT (ng/l) #	2.5 (2.5-4.0)	5.0 (3.0-9.0)	7.0 (4.0-11.0)	6.0 (3.0-9.0)

HF, heart failure; BMI, body-mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UAE, urinary albumin excretion; hs-CRP, highly-sensitive C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-TnT, highly-sensitive troponin T.
* Continuous variables are presented as mean ± standard deviation and compared with the use of Student's t-test, in case of normal distribution. In case of skewed distribution, continuous variables are presented as median (inter-quartile range) and compared using the Kruskall–Wallis test. Binary categorical variables were compared using standard chi-squared tests.
# denotes significant differences were detected between subjects with new onset HFpEF and subjects with new onset HFrEF.

than HFrEF. Figure 2 presents the predicted 10-year cumulative incidences of new onset HFpEF and HFrEF as a function of a subject's age, stratified by gender and UAE level (normal or elevated UAE in their morning urine samples).

Model validation

The mean observed vs. predicted 10-year cumulative incidences were 1.00% vs. 1.07% for new onset HFpEF and 2.12% vs. 2.28% for new onset HFrEF. The calibration plots (Figure 3A and Figure 3B) show a good calibration for both

Table 2 Results from the stratified Weibull proportional hazards model (Equations 1 & 2 in Appendix I)

	[h 1(t)]		[h 2(t)]		[h 3(t)]	
Disease state	HFpEF		HFrEF		Death before HF	
Parameters	Coeffcient (SE)	HR	Coeffcient (SE)	HR	Coeffcient (SE)	HR
a1k (k=1,2,3)	13.027 (2.293)		4.907 (0.932)		6.662 (0.566)	
b1k (k=1,2,3)	89.012 (15.577)		203.811 (71.130)		82.444 (13.851)	
a2k (k=1,2,3)	5.992 (0.749)		3.131 (0.492)		5.742 (0.316)	
b2k (k=1,2,3)	97.936 (37.607)		337.985 (183.188)		81.431 (15.879)	
Female sex			-1.040 (0.176)	0.353	-0.669 (0.102)	0.512
log(UAE)	0.309 (0.077)	1.362			0.128 (0.035)	1.137
Cholesterol			0.148 (0.057)	1.160	0.217 (0.093)	1.242
Glucose					0.042 (0.022)	1.043
log(hs-CRP)	-0.191 (0.099)	0.826			0.148 (0.039)	1.160
log(TGL)					-0.229 (0.099)	0.796
log(NT-proBNP)	0.279 (0.089)	1.321	0.582 (0.059)	1.790	0.185 (0.037)	1.204
hs-TnT DL			-0.184 (0.207)	0.832	-0.156 (0.105)	0.856
log(hs-TnT)			0.393 (0.071)	1.481	0.120 (0.045)	1.127
SBP	0.008 (0.004)	1.008				
Heart rate			0.011 (0.006)	1.011	0.009 (0.004)	1.009
Smoking			0.577 (0.138)	1.781	0.499 (0.080)	1.647
History of MI	0.649 (0.244)	1.914	0.912 (0.155)	2.490	0.368 (0.111)	1.445
BMI	0.087 (0.020)	1.091	0.081 (0.015)	1.084		
History of Stroke					0.597 (0.218)	1.817
LDL					-0.173 (0.092)	0.841
Cystatin C	0.864 (0.462)	2.372			0.759 (0.185)	2.135
log(creatinine)	-1.760 (0.556)	0.172	-0.918 (0.318)	0.399	-0.927 (0.264)	0.396

HF, heart failure; SE, standard error; HR, hazard ratio; UAE, urinary albumin excretion; hs-CRP, highly-sensitive c-reactive protein; TGL, triglycerides; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-TnT, highly-sensitive troponin T; DL, detection limit; SBP, systolic blood pressure; MI, myocardial infarction; BMI, body-mass index; LDL, low-density lipoprotein.

HF outcomes: most of the dots are close to the diagonal line indicating perfect calibration. For the HFrEF outcome, the discriminating ability of our model was moderate with a value of the c statistic of 0.70. The model's discriminative ability for the HFpEF outcome was lower with a c statistic of 0.60.

Software implementation

To allow for convenient application of our risk prediction model in practice, a user-friendly software implementation has been developed in Java. Detailed information is found in the supplementary material online.

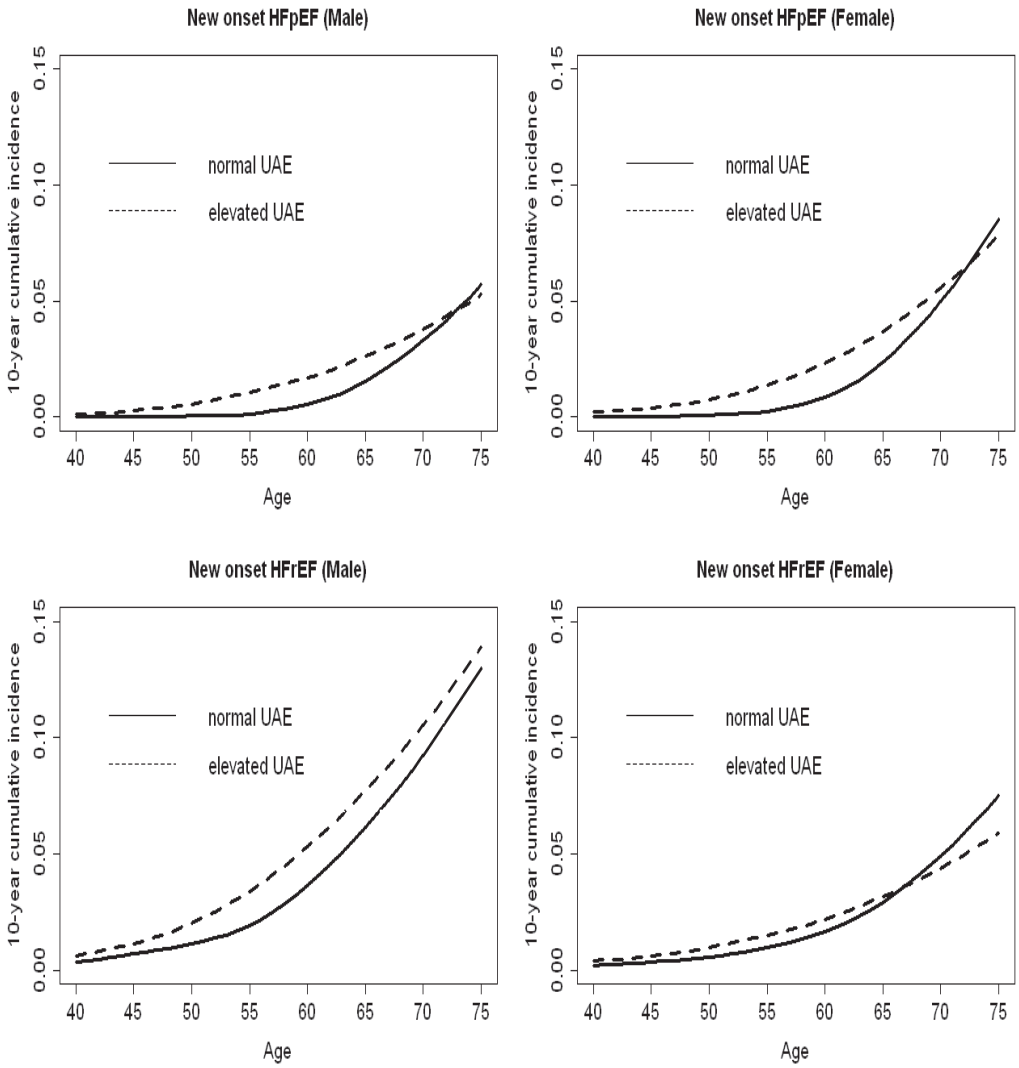

Figure 2 Relationship between a subject's age and predicted 10-year cumulative incidence of new onset HFpEF and HFrEF stratified by both gender (male; female) and UAE level in their morning urine samples (normal UAE; elevated UAE)

Discussion

The PREVEND model presented in this paper is the first heart failure prediction model that differentiates between new onset HFpEF and HFrEF. Using 21 risk factors that are easily available in daily clinical practice, our risk prediction model showed good calibration for both heart failure outcomes. The model's discriminative ability for the two outcomes was poor to moderate, even after inclusion of multiple common risk factors. However, the majority of subjects from the PREVEND study population were at very low risk of developing new onset heart failure. Our model is therefore a suitable tool to

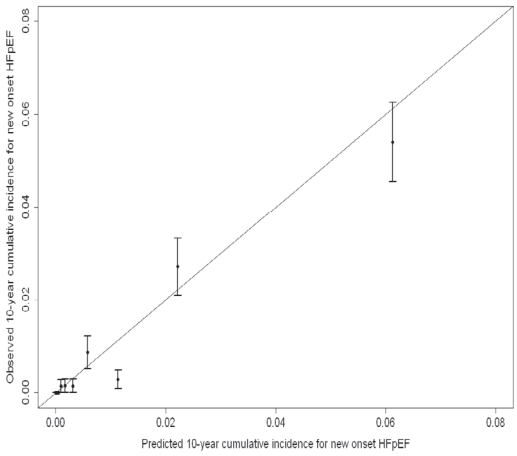

Figure 3A Calibration plot of mean predicted vs. mean observed (1 standard deviation) 10-years cumulative incidence for new onset HFpEF by deciles of predicted cumulative incidence for new onset HFpEF

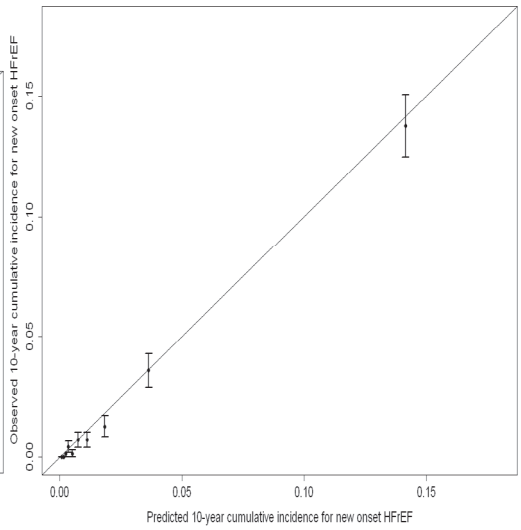

Figure 3B Calibration plot of mean predicted vs. mean observed (1 standard deviation) 10-years cumulative incidence for new onset HFrEF by deciles of predicted cumulative incidence for new onset HFrEF

identify subjects at moderate or high risk of developing HFrEF or HFpEF, but it has little discriminative ability in those at low risk of developing new onset heart failure. Several studies have presented risk models for survival or readmission for patients after diagnosis of heart failure.[23-25] On the other hand, few studies are available with regard to actual prediction of new onset heart failure. Currently, the Framingham Health Study (FHS) and the Atheroscleros Risk in Communities (ARIC) offer the only available risk prediction models for new onset heart failure.[26, 27] However, new diagnostic parameters for heart failure (e.g. natriuretic peptides) have emerged since. In 1999, the FHS has presented the first prediction model for congestive heart failure, predicting new onset heart failure during a four year follow-up period and has been widely used since. Using individuals within the age range of 45-94, significant predictors were age, left ventricular hypertrophy, heart rate, systolic blood pressure, coronary heart disease, valve disease, diabetes, BMI, and vital capactity and cardiomegaly as additional predictors.[26] Another recent prediction model is derived from data of the ARIC study, in which >15,000 subjects aged 45-64 years, were followed for 15 years.[27] The addition of NT-proBNP to their model, using the same variables as the FHS prediction model, increased risk prediction for new heart failure significantly. Both models derived from aforementioned

studies give valuable insight into the pathophysiological processes preceding the first manifestation of heart failure and predict new onset heart failure fairly accurate. However, they are limited by the fact that some predictors are not easily available, such as left ventricular hypertrophy, cardiomegaly or presence of valve disease. This makes these models less applicable in daily practice. Other limitations are the lack of differentiation between HFrEF and HFpEF, and there is no equivalent risk prediction model made using data from European subjects.

There is increasing evidence that HFrEF and HFpEF have different epidemiological profiles and should be considered and treated as separate diseases.[8, 28] Our study confirms these findings by showing that a different set of risk factors is associated with the occurrence of these two outcomes. The incidence of HFrEF, but especially HFpEF, typically increases with age, mainly because of improvements in treatment of underlying co-morbidities. In our model, the effect of age was accounted for by using it as the time scale of the cause specific hazard functions. As a result, although the model was fitted under the assumption that the relative effect of the included cardiovascular risk factors remained constant across time (proportional hazards assumption), the absolute risk of developing new onset heart failure still differed between younger and older subjects.

The strongest predictors specifically for new onset HFpEF were cystatin C and UAE. That decreased renal function, as represented by cystatin C and UAE, was found to be an independent predictor of HFpEF is not new, as previous epidemiologic studies already showed that HFpEF patients more often have decreased renal function, than patients with HFrEF.[8, 28, 29] Finally, we observed a negative association between hs-CRP and new onset HFpEF. Although previous studies have shown increased levels of (hs-)CRP in patients with heart failure compared to heart failure-free subjects,[30-32] CRP had not yet been shown to be associated with increased risk for heart failure. It does have increased risk for mortality. Our findings confirm hs-CRP as a predictor of non-heart failure related mortality.[13, 33] Specific predictors for HFrEF were male gender, cholesterol and smoking. This could well be explained by the ischemic etiology of HFrEF, which occurs in approximately 40% of patients with HFrEF.[9, 34] Further secondary prevention with regard to risk factors for atherosclerotic heart disease might further lower the risk for new onset HFrEF.

Clinical implications

The current risk prediction model showed good calibration, however the model c-statistic showed poor to moderate discrimination. This low discriminative value is remarkable, especially when using multiple common clinical variables. Most, if not all variables are singly and multivariably adjusted associated with new onset heart failure, or specifically with HFrEF or HFpEF.[8, 9] Nonetheless, it appears that even in a large, well-described community-based cohort, with a large well-validated cohort of new onset heart failure, the combination of multiple common clinical variables is insufficient to adequately predict new onset heart failure during long-term follow-up. Therefore, the clinical applicability of the current model remains uncertain, and our results need to be validated and challenged in additional studies. A recently published meta-analysis, reviewing prediction models for mortality in heart failure patients, showed similar model quality, with poor to moderate discrimination of the reviewed risk models, with inconsistent performance.[35] Although there was no differentiation between HFrEF and HFpEF, this postulates that heart failure cohorts consist of a large variety of subjects, with broad differences in clinical and biochemcial characteristics. The large etiologic differences between heart failure patients emphasize distinct pathophysiologic pathways and perhaps differentiating between HFrEF and HFpEF is insufficient to adequatly identify subjects at risk for heart failure.

Strengths and limitations

The large PREVEND cohort, with over 105,000 patient years of follow-up and thoroughly validated cases of new onset heart failure, provides good opportunity for large-scale evaluation of risk factors. In addition, we have identified new onset HFrEF next to HFpEF, giving insight into pathophysiologic pathways for both heart failure phenotypes. Our study is limited by the fact that the PREVEND risk model was not validated in another cohort. Also, PREVEND study subjects are predominantly Caucasian, so our results cannot be extrapolated to subjects of other ethnicities. Finally, the PREVEND cohort was enriched for increased albumin excretion. We therefore conducted stratified analyses, making our results valid for the general population.

Conclusions

The current investigation presents the first available risk prediction model for early identification of subjects at risk for new onset HFrEF and HFpEF. However, with 21 common clinical variables, prediction of new onset heart failure in a community-based cohort, in particular HFpEF, remains difficult.

Supplementary material

Supplementary material is available online.

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Conflict of interest

None declared.

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Appendix I. Details of the competing risks analysis

We used Weibull regression models with a subject's age as the time scale to describe the cause-specific hazard functions of the state transitions included in our model. In particular, for each of the three causes of failure (i.e., new onset HFpEF, new onset HFrEF, and death before the onset of heart failure), the cause-specific hazard functions were expressed as

$$h_k(t;a,b,B,Z) = (a_k / b_k)(t / b_k)^{a_k - 1} \exp(B_k Z_k), k = 1,2,3 \quad (1)$$

where β is a $1 \times m_k$ row vector of regression coefficients and Z is a $m_k \times 1$ column vector that contains the subject's covariate values for the risk factors found to be associated with the *k*-th cause of failure. To account for the overrepresentation of subjects with an elevated UAE in the PREVEND study, the parameters a_k and b_k defining the baseline hazard functions were estimated seperately for subjects with normal and elevated UAE.

Given the cause-specific hazard functions, the cumulative incidence for cause k in the prediction window *w*, i.e., a subject's probability of failing from cause *k* between *A* and *A+w* given that he or she was still event-free at time *A*, where *A* represents the subject's age at the start of the prediction window, can be expressed as

$$P(A < T \leq A + w, D = k | T > A) = \frac{\int_A^{A+w} h_k(s) S(s) d(s)}{S(A)}, k = 1,2; A < A + w \quad (2)$$

$$S(t) = \exp(-\sum_{k=1}^{K} \Lambda_k(t)), k = 1,2,3$$

$$\Lambda_k(t) = \int_0^t h_k(s) d(s), k = 1,2,3$$

where D represents the cause of failure and the subject's overall survival function, with the cumulative cause-specific hazard function of cause *k* up to time t.

Appendix II. List of candidate predictor variables

The following variables were considered as candidate predictors during model building:

- -Sex
- -Body mass index
- -Current smoker or quit smoking <1 year
- -Systolic blood pressure
- -Diastolic blood pressure
- -Heart rate
- -History of myocardial infarction
- -History of stroke
- -History of atrial fibrillation
- -Glucose
- -Cholesterol
- -High-density lipoprotein
- -Low-density lipoprotein
- -Triglicerides
- -Cystatin C
- -Serum creatinine
- -24h urinary albumin excretion
- -Highly-sensitive c-reactive protein
- -N-terminal pro-B-type natriuretic peptide
- -Highly-sensitive troponin T

Part II
Risk factors for cardiovascular disease

Abstract

BACKGROUND: The Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) investigated whether treatment targeted at lowering urinary albumin excretion (UAE) would reduce adverse cardiovascular events. We obtained extended follow-up data to approximately ten years to investigate the long-term effects of fosinopril 20mg and pravastatin 40mg on cardiovascular outcomes in subjects with UAE ≥15mg/24h.

METHODS: The original PREVEND IT consisted of 864 participants and 839 survivors after four years. For every survivor, the primary endpoint determined by the combined incidence of cardiovascular mortality and hospitalization for cardiovascular morbidity, was registered in several national databases and electronic hospital systems.

RESULTS: Mean total follow-up of the extended PREVEND IT was 9.5 years (range 9.4 to 10.7). Four years of treatment with fosinopril was not associated with a reduction in the primary endpoint compared to placebo (HR 0.87; 95%CI 0.61-1.24 [P=0.42]) during long-term follow-up. After 9.5 years, subjects with a baseline UAE in the upper quintile (≥50mg/24hrs) had a total event rate of 29.5% and were at a higher risk of developing cardiovascular disease compared to less UAE (HR 2.03; 95%CI 1.38-2.97 [P<0.01]). In addition, four years of fosinopril treatment resulted in a risk reduction of 45% (95%CI 6%-75% [P=0.04]) in this group compared to placebo. Subjects originally assigned to pravastatin had no overall risk reduction in the primary endpoint (p=0.99).

CONCLUSIONS: Elevated UAE is associated with increased cardiovascular mortality and morbidity after 9.5 years of follow-up, with a doubling of the risk if the UAE is ≥50mg/24h. In this group, the benefits of four year treatment with fosinopril were sustained during post-trial follow-up for cardiovascular mortality and morbidity. We propose that UAE be used to estimate risk in the general population and that large clinical trials be designed to confirm the hypothesis that ACE-inhibitor treatment may be beneficial in patients with mildly elevated UAE despite the absence of other co-morbidities.

Chapter 6

Long-term effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Ten years of follow-up of PREVEND IT

Frank P. Brouwers
Folkert W. Asselbergs
Hans L. Hillege
Rudolf A. de Boer
Ron T. Gansevoort
Dirk J. van Veldhuisen
Wiek H. van Gilst

American Heart Journal 2011;161(6):1171-8

Introduction

Microalbuminuria (MA) is associated with an increased risk of cardiovascular morbidity and mortality, both in patients with an increased risk profile[1, 2] and in the general population.[3, 4] The Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) was a double-blind, randomized, placebo-controlled trial to determine whether the ACE-inhibitor fosinopril and the HMGCoA-reductase inhibitor pravastatin would reduce the incidence of cardiovascular death and hospitalization for cardiovascular morbidity in a microalbuminuric population without hypertension and /or hypercholesterolaemia.[3, 5] It was demonstrated that treatment with fosinopril significantly lowered blood pressure and urinary albumin excretion (UAE) and was associated with a trend in reducing cardiovascular events in subjects with UAE ≥15mg/24h and a significant reduction in subjects with a higher UAE (≥50mg/24h). Pravastatin significantly lowered total and LDL cholesterol, but had no significant effect on UAE and / or prognosis.

Due to the inclusion of relatively low risk subjects, the rate of cardiovascular adverse events was lower than expected. Therefore, the original PREVEND IT was underpowered in demonstrating a significant effect of treatment on clinical outcome. Other clinical trials such as the West of Scotland Coronary Prevention Study (WOSCOPS),[6] HOPE,[7] and SOLVD[8] showed preservation of clinical benefit by the assigned treatment of up to several years after the trial was ended, despite the fact that the large majority of patients were taken off study medication. Therefore, in order to assess the long-term risk of our study population and whether the beneficial effects of treatment in the group with UAE ≥50mg/24h was preserved, we extended the follow-up of the original PREVEND IT by six years, to approximately 10 years.

Methods

Design

PREVEND IT is an investigator-initiated, single-center, double-blind, randomized, placebo-controlled trial with a 2x2 factorial design to assess the value of microalbuminuria as an indicator of increased cardiovascular risk in the general population. Subjects were randomized to 20mg fosinopril or matching placebo, and to 40mg pravastatin or matching placebo. Details of the PREVEND IT objectives, design, methods, and main results have been

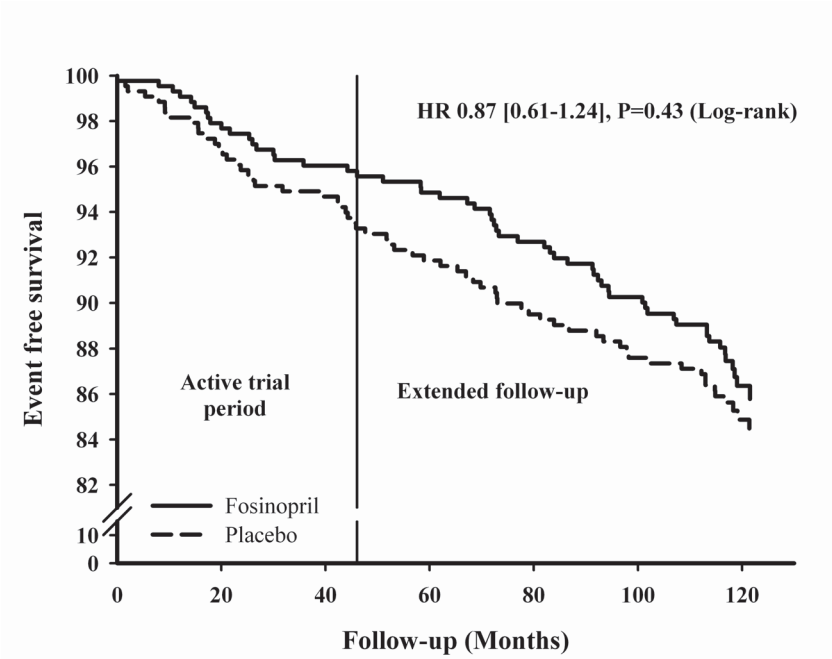
reported previously.[5] Briefly, the key entry criteria of the PREVEND IT were persistent microalbuminuria (one urinary albumin concentration ≥10 mg/l in an early morning spot urine test and at least one 15 to 300 mg/24h in two 24h urine samples), absence of antihypertensive and lipid-lowering medication, a blood pressure of <160/100 mmHg and total cholesterol of <8.0 mmol/l or <5.0 mmol/l in the case of previous myocardial infarction. From April 1998 to June 1999, 864 subjects were included in the PREVEND IT and were randomized to study medication for the duration of four years (referred to as "active trial period"). At the end of this four year period, all subjects were taken off study medication and returned to the care of their general practitioners. We extended the follow-up for an additional 5.5 years after the active trial period was ended, resulting in a total follow-up time of 9.5 years. An independent data and safety monitoring committee regularly monitored the progress of PREVEND IT during the entire follow-up period. The study was approved by the Institutional Review Board and was conducted in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all subjects before randomization.

Endpoint collection and follow-up

Follow-up was extended to 1 January 2009, an average of 5.5 years after the end of the active trial period. The composite primary endpoint is similar to the active trial.[5] Mortality was divided into non-cardiovascular versus cardiovascular deaths. Documented hospitalization for cardiovascular morbidity was subdivided into nonfatal myocardial infarction, myocardial ischemia, heart failure, peripheral vascular disease and cerebrovascular accident.

Every surviving participant had a final visit three months following the end of the active trial period. Thereafter, a large proportion of the study subjects continued their participation in the ongoing PREVEND-program (N = 530) and visited the outpatient clinic every three to four years.[3] Follow-up for all other surviving subjects (N = 271) was collected via personal communication and electronic hospital files. Data on mortality were retrieved from the municipal register. Cause of death was obtained through the Dutch Central Bureau of Statistics and was coded according to the 10th revision of the International Classification of Diseases. Follow-up on hospitalization for cardiovascular morbidity was derived from records held by PRISMANT, the Dutch national registry of hospital discharge

A



B

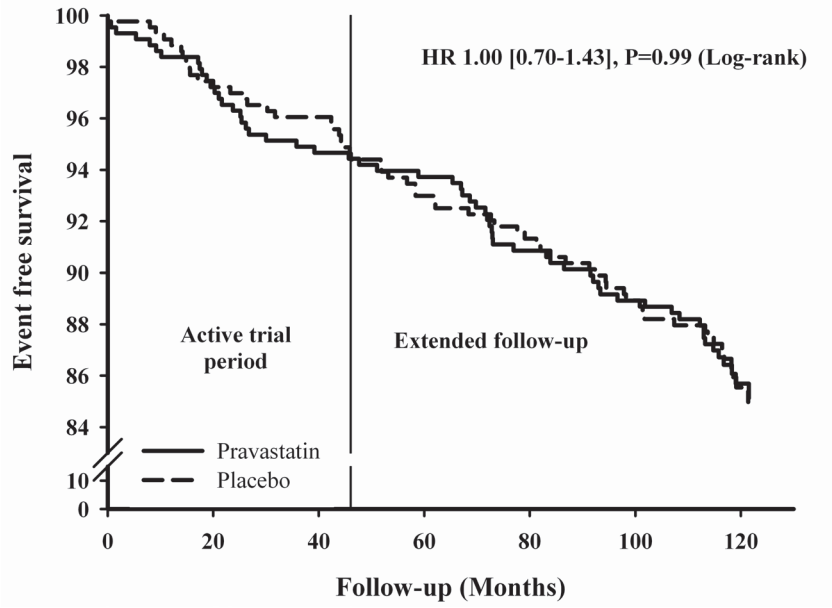


Figure 1 Primary endpoint Kaplan-Meier estimates of incidence of cardiovascular events in fosinopril and matching placebo (A) and pravastatin and matching placebo group (B). Hazard ratios (HR) and 95% CIs are given.

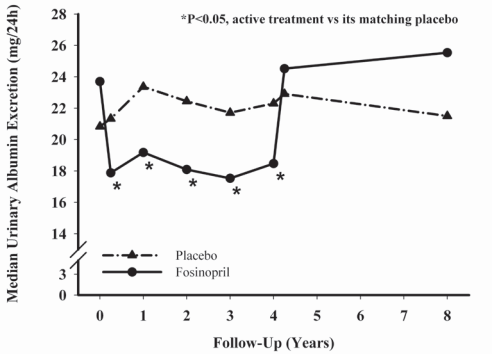


Figure 2A Median urinary albumin excretion (mg/24h) by treatment and visit.

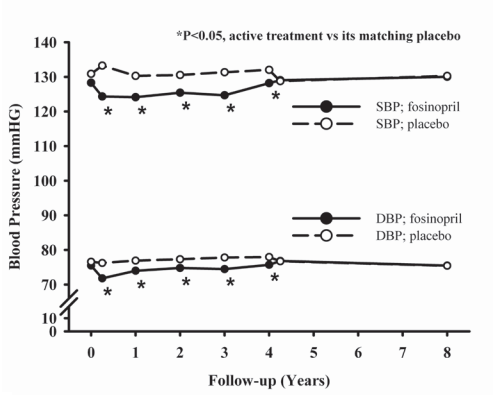


Figure 2B Mean blood pressure by treatment and visit.
SBP=systolic blood pressure; DBP=diastolic blood pressure.

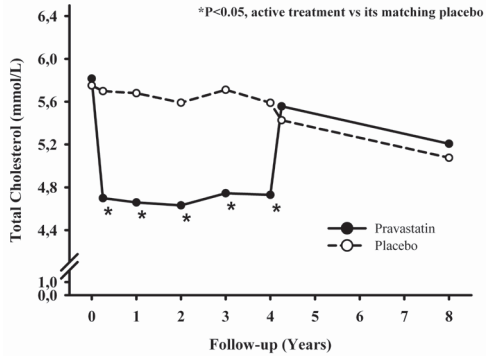


Figure 2C Mean total cholesterol levels by treatment and visit.

diagnoses. In addition, personal communication was used to obtain data from subjects lost to follow-up. The date of admission was used as the date of the event. Details of each cardiovascular event were obtained from the treating physician. The independent endpoint committee of the active trial period reviewed all endpoints and the members had no knowledge of subject's treatment assignments.

At follow-up visits in the ongoing PREVEND program, various clinical and biochemical measurements were performed and two 24h urine collections

were obtained. Systolic and diastolic blood pressure measurements were calculated as the mean of the last two of ten consecutive measurements with an automatic Dinamp XL model 9300 series device (Johnson-Johnson Medical Inc). Plasma glucose, serum total and LDL cholesterol, and serum creatinine were determined by Kodak Ektachem dry chemistry (Eastman Kodak). Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/l and intra-assay and interassay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic).

Table 1 Baseline Characteristics of PREVEND IT (N = 864)

	Fosinopril		Pravastatin	
Variables	Placebo (N = 433)	Active (N = 431)	Placebo (N = 431)	Active (N = 433)
Age (years)	51.5±11.4	51.1±12.2	50.5±11.7	52.1±11.9
Male Gender (%)	63.7	66.1	62.2	67.7
White (%)	97.0	95.1	96.8	95.4
Smoking (%)				
Past	31.4	34.4	34.1	31.6
Current	43.6	36.2	37.6	42.3
Systolic blood pressure (mmHg)	131±18	129±17	130±17	131±18
Diastolic blood pressure (mmHg)	76±10	76±10	76±10	77±10
Cholesterol (mmol/l)				
Total	5.7±1.0	5.8±1.1	5.8±1.0	5.8±1.0
HDL	1.0±0.4	1.0±0.3	1.0±0.4	1.0±0.3
LDL	4.0+0.9	4.1±1.0	4.0±1.0	4.1±1.0
Triglycerides (mmol/l)	1.3 (0.9-1.9)	1.4 (0.9-2.0)	1.3 (0.9-1.9)	1.4 (0.9-2.0)
Glucose (mmol/l)	5.0±1.2	4.9±1.0	4.9±0.9	5.0±1.2
Serum creatinine (µmol/l)	89±14	92±14	90±14	91±14
Albuminuria (mg/24h)	22.1 (15.3-39.4)	23.5 (16.8-43.9)	23.5 (16.1-42.5)	22.2 (15.6-40.8)
Body mass index (kg/m^2)	26±5	26±4	26+4	26+4
Diabetes Mellitus (%)	2.8	2.3	2.3	2.8
Prior event (%)	2.5	4.2	4.4	2.3
Myocardial Infarction (%)	0.2	0.7	0.7	0.2
Angina Pectoris (%)	0.5	0.7	0.5	0.7
Coronary angioplasty of bypass (%)	0.5	1.2	0.9	0.5
Heart Failure (%)	0.0	0.0	0.0	0.0
Cerebrovascular accident (%)	0.2	1.4	1.2	0.5
Peripheral vascular disease (%)	0.5	0.7	0.7	0.5
Aspirin and antiplatelet agents (%)	2.8	2.1	3.5	1.4
Beta-Blockers (%)	1.4	0.7	1.4	0.7
Nitrate (%)	0.5	0.5	0.9	0.0
Diuretics (%)	0.7	0.7	0.9	0.5
Calcium channel blockers (%)	0.9	0.9	1.2	0.7
Digoxin (%)	0.9	0.7	0.9	0.7

Statistical analysis

Baseline characteristics are given as mean ± standard deviation. In case of a skewed distribution, the median (interquartile range) was used. Two-way ANOVA was used firstly to test whether the dependent variable changed significantly with each of the two treatments while taking into account the effects of the other treatment, and secondly, to test whether the effect of fosinopril, for example, did not depend on pravastatin. Because of the skewed distribution, UAE was transformed to natural logarithm. Time to first occurrence of outcome are presented as Kaplan-Meier estimates, and statistical differences between placebo and active treatment were analyzed by log-rank. Furthermore, results are summarized by hazard (risk) ratios or relative risks with 95% CIs based on robust standard error estimates. The impact of baseline UAE was evaluated by dichotomization of the parameter into the lowest four quintiles against the highest quintile (UAE ≥50mg/24h) as was done during the active trial.[5] All analyses were by design performed on an intention-to-treat basis, unless stated otherwise. Probability values were two-sided and were required to be <0.05 to be significant. All calculations were performed with SPSS version 16 software.

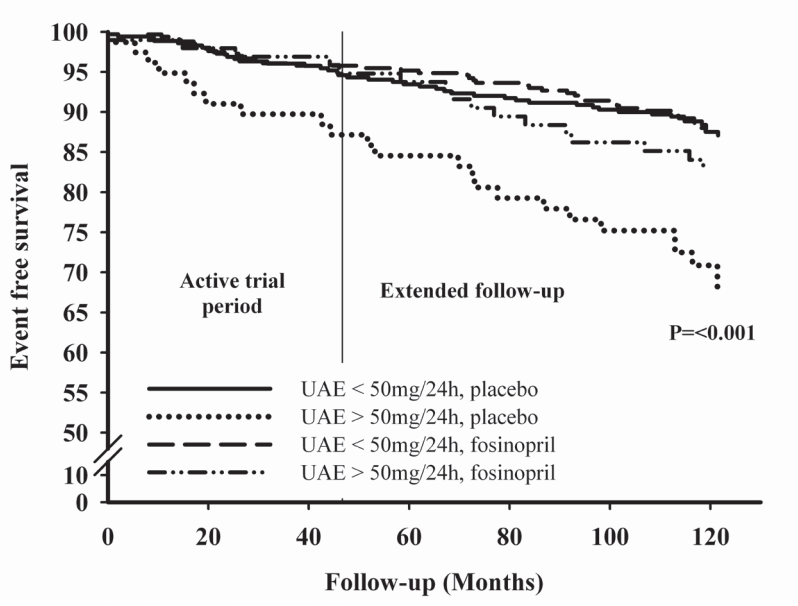


Figure 3 Primary endpoint in UAE ≥50mg/24h Kaplan-Meier estimates of incidence of cardiovascular events in the fosinopril and placebo group, divided by a UAE more than or less then 50mg/24h.
*compared to UAE≥50mg/24h, fosinopril

Table 2 Total event outcome

	Total Follow-up period			
	Fosinopril		Pravastatin	
	Placebo (N = 431)	Active (N = 431)	Placebo (N = 431)	Active (N = 431)
Primary endpoint *				
no. (%)	64 (14.8)	56 (13.0)	60 (13.9)	60 (13.9)
Hazard Ratio [95% CI]	1.00	0.86 [0.60-1.23]	1.00	1.01 [0.71-1.44]
p value		0.42		0.97
Mortality				
All causes				
no. (%)	32 (7.4)	35 (8.1)	29 (6.7)	38 (8.8)
Hazard Ratio [95% CI]	1.00	1.08 [0.67-1.74]	1.00	1.32 [0.82-2.14]
p value		0.77		0.26
Cardiovascular causes				
no. (%)	12 (2.8)	9 (2.1)	11 (2.6)	10 (2.3)
Hazard Ratio [95% CI]	1.00	0.74 [0.31-1.75]	1.00	0.92 [0.39-2.16]
p value		0.49		0.84
Hospitalization for				
Nonfatal myocardial infarction and/or – ischaemia				
no. (%)	32 (7.4)	34 (7.9)	36 (8.4)	30 (6.9)
Hazard Ratio [95% CI]	1.00	1.05 [0.65-1.70]	1.00	0.84 [0.52-1.36]
p value		0.84		0.47
Heart Failure				
no. (%)	3 (0.7)	1 (0.2)	1 (0.2)	3 (0.7)
Hazard Ratio [95% CI]	1.00	0.33 [0.03-3.18]	1.00	3.02 [0.31-28.99]
p value		0.34		0.34
Peripheral vascular disease				
no. (%)	8 (1.8)	6 (1.4)	7 (1.6)	7 (1.6)
Hazard Ratio [95% CI]	1.00	0.74 [0.26-2.14]	1.00	1.00 [0.35-2.86]
p value		0.58		1.00
Cerebrovascular accident				
no. (%)	19 (4.4)	12 (2.8)	14 (3.2)	17 (3.9)
Hazard Ratio [95% CI]	1.00	0.63 [0.30-1.29]	1.00	1.22 [0.60-2.47]
p value		0.21		0.59
Total cardiovascular morbidity †				
no. (%)	59 (13.6)	53 (12.3)	56 (13.0)	56 (12.9)
Hazard Ratio [95% CI]	1.00	0.89 [0.61-1.29]	1.00	1.00 [0.69-1.45]
p value		0.54		0.99

* The sum of all events does not compute with the total number given, because multiple events in one subjects are counted as one.
† $P<0.05$ active medication vs. placebo

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Results

Baseline characteristics of all randomized subjects are summarized in Table 1. These characteristics represent the PREVEND IT population at the beginning of the active trial period in 1997 and show a middle-aged population with a low prevalence of conventional cardiovascular risk factors, cardiovascular history or use of cardiovascular drugs. Mean follow-up was 9.5 years (range 9.4 to 10.7) from the start of the trial to 1 January 2009. Due to emigration, two subjects (0.2%) were lost to follow-up. Alongside study drugs, open label ACE-inhibitor usage was 0.0%, 4.3% and 10.6% at baseline screening, four and eight years later, respectively, for the entire study population. For statin usage, this was 0.0%, 3.2% and 11.6%. Rate of ACE-inhibitor and statin use remained similar in all former randomized groups during the entire follow-up period.

The incidence of the primary endpoint increased from 5.2% in the active trial to 13.9% after 9.5 years of follow-up. Subjects assigned to fosinopril during the active trial period had a non-significant risk reduction of 13% (HR 0.87; 95%CI 0.61-1.24 [P = 0.42]) during the entire follow-up period, which is in accordance with a number needed to treat (NNT) of 55 subjects for 9.5 years. Subjects originally assigned to pravastatin had no risk reduction during the entire follow-up period (HR 1.00; 95%CI 0.70-1.43 [P = 0.99], NNT = 1555), as shown in Figures 1A and 1B. An overview of outcomes is shown in Table 2. Both fosinopril and pravastatin use was not associated with a significant risk reduction for a specific endpoint. 67(7.8%) subjects died during the entire follow-up period. Both fosinopril (P=0.77) as pravastatin

Table 3 UAE≥15mg/24h vs. UAE≥50mg/24h

	UAE≥15mg/24h			UAE ≥50mg/24h		
	Placebo (N = 433)	Fosinopril (N = 431)	HR [95% CI]	Placebo (N = 78)	Fosinopril (N = 98)	HR [95% CI]
Primary endpoint	64 (14.8%)	56 (13.0%)	0.87 [0.61-1.24]	23 (29.5%)	16 (16.3%)	0.51 [0.27-0.97] *
Mortality						
All causes	31 (7.2%)	32 (7.4%)	1.02 [0.62-1.67]	11 (14.1%)	8 (8.2%)	0.54 [0.22-1.35]
CV causes	12 (2.8%)	11 (2.6%)	0.74 [0.13-1.76]	5 (6.4%)	3 (3.1%)	0.45 [0.11-1.88]
Hospitalization for						
Non fatal MI	32 (7.4%)	34 (7.9%)	1.05 [0.65-1.70]	10 (12.8%)	11 (11.2%)	0.80 [0.34-1.89]
Heart failure	3 (0.7%)	1 (0.2%)	0.33 [0.03-3.18]	2 (2.6%)	0 (0.0%)	0.01 [0.00-1198.48]
PVD	8 (1.8%)	6 (1.4%)	0.74 [0.26-2.14]	3 (3.8%)	1 (1.0%)	0.24 [0.03-2.31]
CVA	19 (4.4%)	12 (2.8%)	0.63 [0.30-1.29]	6 (7.7%)	3 (3.1%)	0.38 [0.10-1.53]
Total CV morbidity	59 (13.6%)	53 (12.3%)	0.89 [0.61-1.29]	21 (26.9%)	15 (15.3%)	0.53 [0.27-1.02]

* $P < 0.05$

UAE denotes urinary albumin excretion; HR hazard ratio; CV cardiovascular, MI myocardial infarction; PVD peripheral vascular disease; CVA cerebrovascular accident

(P=0.26) showed no significant reduction in total mortality compared to placebo. Regarding cardiovascular mortality (N = 21; 2.4%), treatment with either fosinopril (HR 0.74; 95%CI 0.31 to 1.76 [P = 0.49]) or pravastatin (HR 0.92; 95%CI 0.39 to 2.16 [P = 0.84]) had no significant beneficial effect (see Table 2).

At the end of the active trial period, the median UAE was significantly lowered in the fosinopril group compared to placebo (P<0.05). Three months after cessation of fosinopril, median UAE had increased significantly from 18.5 to 24.5mg/24h (IQR 13.3-51.2, [P<0.01]) and remained stable during extended follow-up, as shown in Figure 2A. Regarding blood pressure, a significant decrease in systolic and diastolic blood pressure was achieved with fosinopril during the active trial period compared to placebo. Three months after stopping fosinopril, blood pressure returned to baseline levels and remained stable during extended follow-up, as illustrated in Figure 2B. In the group originally assigned to pravastatin, blood pressure and UAE levels were unaffected by treatment compared to placebo and remained stable during extended follow-up.

A similar development occurred with total and HDL cholesterol levels. After a significant decrease by statin treatment compared to placebo, total cholesterol and HDL cholesterol returned to baseline levels three months after the active trial period. Levels of total cholesterol remained stable during extended follow-up, refer to Figure 2C. Fosinopril had no effect on cholesterol levels over the entire follow-up period compared to matching placebo.

Subjects with a UAE in the upper quintile (≥50mg/24h, median 77.7mg/24h) were at increased risk of developing a cardiovascular event compared to subjects with lower UAE (<50mg/24h, median 19.3mg/24h) during long-term follow-up (HR 2.03; 95%CI 1.38-2.97 [P<0.01]). Additionally, subjects with UAE ≥50mg/24h and originally assigned to fosinopril, had a reduction in incidence of the primary endpoint from 29.5% to 16.3% (HR 0.51; 95%CI 0.27-0.97 [P=0.04]) during 9.5 years of follow-up (refer to Table 3). This is in accordance with NNT=8 subjects for 9.5 years. Furthermore, subjects with UAE ≥50mg/24h originally endpointy assigned to the placebo group were almost three times more at risk compared to the fosinopril group (Figure 3: HR 2.87; 95%CI 1.72-4.79 [P<0.01]).

Discussion

This extended follow-up of the PREVEND IT reports on two major findings: 1) Elevated UAE (≥15mg/24h) is associated with increased cardiovascular mortality and morbidity (13.9%) in apparently healthy subjects without any other indication for primary prevention, after 9.5 years of follow-up. In addition, this risk doubles if the UAE is ≥50mg/24h (29.5%). 2) Treatment with fosinopril during the active trial period significantly reduced mortality and morbidity in the group of subjects with UAE ≥50mg/24h, thereby lowering their level of risk to subjects with lower UAE, which has been reported previously.[5] This benefit persisted and was even more pronounced during long-term follow-up, despite a similar rate of ACE-inhibitor use after the end of the active trial period.

In our view, these findings support our hypothesis that elevated UAE, also below the conventional microalbuminuria cut-off values of 30-300mg/24h is an unfavorable marker for the development of cardiovascular disease after long-term follow-up, even in the absence of other cardiovascular risk factors. In addition, the protective effect of fosinopril treatment during the active trial period most likely underestimates the effects of a more prolonged treatment. In the case of pravastatin, however, our results after 9.5 years of follow-up show no direct effect on UAE. With evaluation of the effect of pravastatin on outcome, we see trend for a slightly lowered risk reduction for cardiovascular mortality and hospitalization for nonfatal myocardial infarction and / or ischemia.

Several trials have indicated that microalbuminuria is associated with a more adverse cardiovascular outcome.[4, 9, 10] However, treatment aimed at reducing cardiovascular events by lowering UAE in a general population, with no indication for preventive treatment, was only investigated in PREVEND IT. While the event-rate during the active trial period was lower than expected, we observed an event rate of 13.9% after 9.5 years of follow-up, increasing power and providing corroborative evidence of UAE for being an important additional marker of early cardiovascular disease, in the absence of other cardiovascular risk factors.

The initial report of PREVEND IT showed that treatment with fosinopril was associated with a trend in reducing cardiovascular events.[5] During the extended follow-up presented herein, a postponed benefit of four years treatment with fosinopril and/or pravastatin was not observed. However, fosinopril showed a long-term beneficial effect in subjects with an UAE ≥50mg/24h, which confirms

the observations from the active trial period. This outcome is in accordance with results of other extended trials with ACE-inhibitors, like the extended HOPE.[7]

It remains unclear why ACE-inhibitors would exert beneficial effects even long after cessation after the active trial period. One possible explanation could be that ACE-inhibitors cause structural changes, which persist after cessation of the drug. PREVEND IT provides some unique insights to verify this hypothesis. It was observed that after the active trial period, levels of UAE and blood pressure rapidly returned to their baseline levels in the subjects who received fosinopril for four years, as shown in Figure 2A-B. These findings indicate that the beneficial effects of fosinopril on lowering albuminuria and blood pressure diminish directly after cessation.

For subjects with UAE ≥50mg/24h, fosinopril treatment significantly reduced the incidence of the primary endpoint compared with lower UAE levels, even after stopping study medication. The survival curves tend to become parallel during the extended trial period, but do not converge after long-term follow-up. Since blood pressure and UAE levels returned to normal directly after drug cessation, there may be other mechanisms underpinning this observation, for example potential long-term vascular and cardiac preservation via neurohormonal factors, or preservation of endothelial integrity and function, all exerting protective effects long after fosinopril had been stopped.

The results of PREVEND IT are in line with various additional trials, which show a beneficial effect of ACE-inhibitors on cardiovascular disease[7, 11-14] and long-term post-trial benefits which have been reported.[8, 15, 16] However, these studies focus mostly on diabetics,[17, 18] subjects with chronic kidney disease[19] or heart failure,[20] whereas PREVEND IT targets asymptomatic subjects with only slightly elevated levels of UAE. In addition, only a very few number of trials since PREVEND IT have focused on UAE targeted therapy to prevent cardiovascular disease. The PEACE trial, which was performed in a population with stable coronary artery disease, reported similar results. The effect of treatment with the ACE-inhibitor trandolapril increased as the estimated glomerular filtration rate (eGFR) decreased.[12, 21] Since the overall renal function in PEACE was relatively high, just as in PREVEND IT, treatment with trandolapril showed lack of benefit over the entire cohort. The MICRO-HOPE trial examined diabetic subjects with documented cardiovascular disease and a beneficial effect of ramipril on

cardiovascular outcome was observed.[22] Our analysis shows that similar effects may be obtained in subjects at a substantially lower risk level than those subjects studied in previous trials. In addition, four years of treatment with fosinopril significantly reduces cardiovascular events in subjects with an UAE ≥50mg/24h during long-term follow-up. This underscores the notion that UAE targeted therapy may be beneficial not only in subjects with hypertension, diabetes mellitus or chronic kidney disease, but also in aparently healthy subjects with UAE ≥50mg/24h.

Study limitations

At the end of PREVEND IT, a modest crossover between treatment groups was present. However, the absolute crossover numbers are limited and if there was any effect of this crossover, it would cause an underestimate of our results. Also, drug exposure during extended follow-up, after the study medication was stopped, may have influenced the outcome. The study population in this trial was at fairly low risk. Less than 3% of the participants were diabetic and evidence of prior cardiac events such as myocardial infarction, bypass surgery or heart failure were all less than 1% each. Given the low risk of this population, the number of cardiovascular events was consequently low. The sample size of 864 subjects was also modest, making this study underpowered to demonstrate a beneficial effect of treatment on outcome.

Conclusions

Elevated UAE is associated with a significant increase in cardiovascular mortality and morbidity with doubling of the risk if the UAE is ≥50mg/24h. In this group, treatment with fosinopril significantly reduced mortality and morbidity. This benefit persisted during and was even more pronounced after the entire follow-up period when compared to the active trial period. We propose that UAE be used to estimate risk in the general population and that large clinical trials be designed to confirm the hypothesis that ACE-inhibitor treatment may be beneficial in patients with mildly elevated UAE despite the absence of other co-morbidities.

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Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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Abstract

OBJECTIVE: Experimental studies have shown that adrenomedullin (ADM) plays animportant role in circulatory homeostasis. Mid-regional pro-ADM (MR-proADM) is a stable form of ADM. Observational studies found an important association with age, BMI and kidney function. We aim to evaluate the prognostic performance of MR-proADM in the general population, controlling for these potential confounders.

DESIGN: Prospective cohort study

METHODS: We studied 7,903 subjects (mean age 49±13 years, 49% male) derived from the Prevention of REnal and Vascular ENdstage Disease (PREVEND) cohort, with a median follow-up of 10.5 years.

RESULTS: Mean baseline MR-proADM was 0.39±0.14 nmol/l. In cross-sectional analyses, age, blood pressure, C-reactive protein, cystatin C, N-terminal pro-B-type natriuretic peptide and urinary albumin excretion remained as independent determinants of MR-proADM. In prospective analyses, MR-proADM was associated with the primary endpoint (combined cardiovascular mortality and cardiovascular morbidity), with event rates ranging from 8% in the lowest quintile to 45% in the highest quintile, (P for trend <0.001), independent of age, sex, components of the Framingham Risk Score (FRS) and other cardiovascular markers. Overall Net Reclassification Improvement against the FRS was 2.2%, which was non-significant. We, however, observed significant modification of the effect of MR-proADM on outcome by age. In subjects ≤70years (N = 7,475), 8.8% was correctly reclassified in a higher risk category (P=0.017) and 3.4% to a lower risk category (P<0.001). In subjects >70years (N = 428) there was no improvement of reclassification (P=0.32).

CONCLUSION: This study gives a detailed overview of the distribution of ADM in a general population and provides evidence of ADM as a potent and interesting biomarker in predicting cardiovascular events. These results seem especially applicable to younger subjects.

Chapter 7

Influence of age on the prognostic value of mid-regional pro-adrenomedullin in the general population

Frank P. Brouwers
Rudolf A. de Boer
Pim van der Harst
Joachim Struck
Paul E. de Jong
Dick de Zeeuw
Rijk O. Gans
Ron T. Gansevoort
Hans L. Hillege
Wiek H. van Gilst
Stephan J. Bakker

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Introduction

Adrenomedullin (ADM) was first discovered in the early nineties in phaeochromocytoma cells.[1] It is a multifunctional, 52 amino acid peptide hormone expressed in numerous tissues.[2] It is thought to originate primarily in endothelial cells, where cellular stress, ischemia and hypoxia result in increased expression,[2] together with nitric oxide and endothelin.[3] The physiological function of ADM is still under investigation, but it has been suggested it exerts effects similar to those of brain-type natriuretic peptide (BNP) and atrial natriuretic peptide (ANP).[4, 5] It is capable of promoting vasorelaxation, natriuresis, diuresis and cardiac output, thus contributing to maintaining circulatory homeostasis.[6, 7] A substantial amount of data also suggests that ADM acts as a protective factor for blood vessels, primarily by counteracting vascular damage and remodelling.[3, 8] These qualities make ADM an interesting candidate novel biomarker for cardiovascular (CV) outcome.

The mid-regional portion of pro-adrenomedullin (MR-proADM) is more stable than ADM and therefore better suited for clinical practice and assessment in stored samples.[9] MR-proADM is elevated in females and increases with age.[10] It is also elevated in subjects with hypertension and has prognostic value for CV mortality and morbidity in subjects with myocardial infarction,[11-13] heart failure,[13-15] chronic kidney disease[6] as well as subjects with hypertension and increased left ventricular mass.[16] MR-proADM was recently shown to be effective in predicting 90-day mortality risk in patients admitted with acute heart failure, with additive prognostic value over BNP alone.[17] Epidemiologic data on MR-proADM levels in the general population remain scarce, with published data from only one cross-sectional study.[10] The present study aims to provide insight into the distribution of MR-proADM and investigate its prognostic performance for CV mortality and morbidity in the general population. Observational studies show an important association with age, body mass index (BMI) and kidney function,[10, 18] but it is unclear whether these associations affect the predictive value of MR-proADM for CV outcome. In addition, the prognostic value and potential additive value of MR-proADM are compared to those of conventional CV risk factors (Framingham Risk Score, FRS) and adjusted for novel and relevant covariates, including N-terminal-proBNP (NT-proBNP), urinary albumin excretion (UAE) and highly-sensitive C-reactive protein (hs-CRP).

Methods

Study population

This study was performed in subjects participating in the Prevention of REnal and Vascular ENdstage Disease (PREVEND) study.[19] The objective of the PREVEND program is to prospectively investigate the natural course of increased levels of UAE and assess the value of microalbuminuria as an indicator of increased CV and renal risk in the general population. Details of PREVEND have been described elsewhere.[19-21] In summary, from 1997 to 1998, all inhabitants of the city of Groningen, The Netherlands, aged 28 to 75 years (N = 85,421) were asked to send in a morning urine sample and complete a short questionnaire on demographics and CV history. Response was received from 40,856 subjects (47.8%). All subjects with a UAE ≥10 mg/l (N = 7,786) in their morning urine together with a randomly selected control group with a urinary albumin concentration <10 mg/l (N = 3,395) were invited to the outpatient clinic. After exclusion of subjects with insulin-dependent diabetes mellitus, pregnant women, and men and women unable or unwilling to participate, a total of 8,592 subjects completed the screening program, as shown in Figure 1. 7,903 individual blood samples, taken at baseline, were suitable for analysis of MR-proADM levels and eligible for the current analysis. The PREVEND study was approved by the local medical ethics committee and conducted in accordance with Declaration of Helsinki guidelines. All subjects provided written informed consent.

Assays

Plasma samples were drawn from all PREVEND participants at baseline and aliquots were stored at -80°C prior to analysis. Detection of MR-proADM was performed using a immunoassay (B.R.A.H.M.S., GmbH/ThermoFisher Scientific, Hennigsdorf, Germany).[9] The interassay coefficients of variation was <20% for values >0.12nmol/l (analytical range 0.08-14.7nmol/l). NT-proBNP measurements were performed in plasma on an ElecsysTM 2010 analyser, a commercially available electrochemiluminescent sandwich immunoassay (Elecsys proBNP, Roche Diagnostics, Mannheim, Germany).[22] The intra- and interassay coefficients of variation were 1.2-1.5% and 4.4-5.0%, respectively (analytical range 5-35.000 pg/ml). UAE, hs-CRP and serum cystatin C were determined by nephelometry (BNII, Dade Behring Diagnostic, Marburg, Germany). Intra- and interassay coefficients of variation were less than 2.2%

and 2.6% for UAE, respectively; less than 4.4% and 5.7% for hs-CRP, respectively; and less than 4.1% and 3.3% for cystatin C, respectively. Serum creatinine, plasma cholesterol and glucose were determined in one laboratory by Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY, USA), using an automated enzymatic method. The intra- and interassay variation coefficient of serum creatinine were respectively 0.9% and 1.1%. Serum triglycerides were measured enzymatically. A commercially available assay system was used to assess high-densitiy lipoprotein (HDL) cholesterol (Abbott Inc., Abbott Park, IL, USA).

Risk factor definition

Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or the use of antihypertensive medication. BMI was calculated as the ratio of weight to height squared (kg/m^2). Hypercholesterolemia was defined as total serum cholesterol of >6.5 mmol/l (251 mg/dl) or the use of lipid-lowering therapy. Diabetes was defined as fasting plasma glucose >7.0 mmol/l (126 mg/dl) or non-fasting plasma glucose >11.1 mmol/l or the use of antidiabetic medication. Estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease

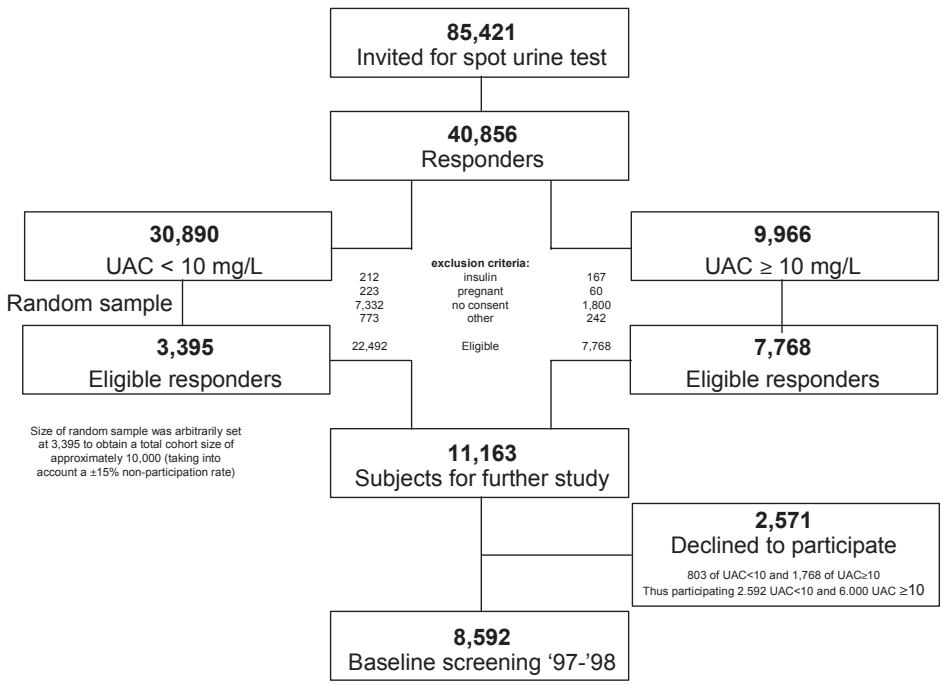

Figure 1 Flow chart of the formation of the PREVEND Cohort.

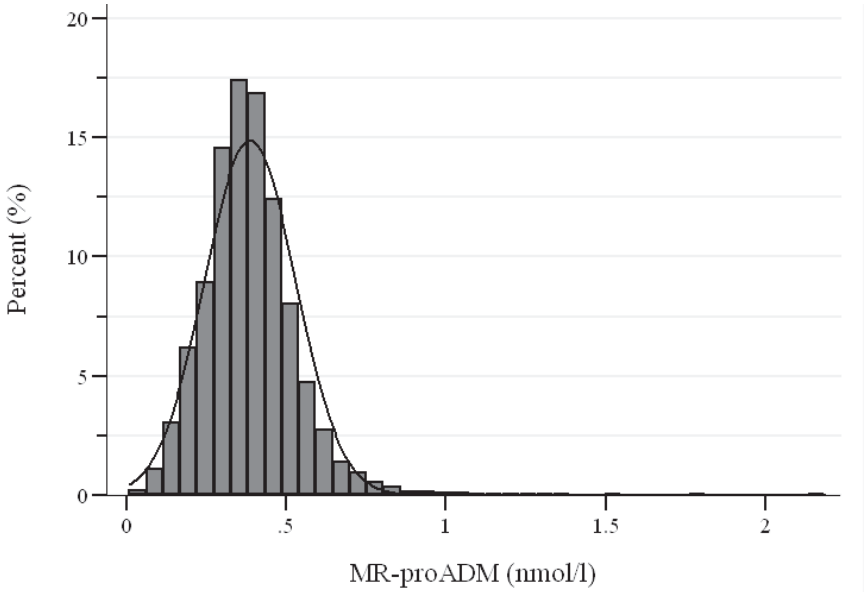

Figure 2 The distribution of MR-proADM in PREVEND.

(sMDRD) formula.[23] Smoking was categorized as no smoking, or smoking (current or stopped <1 year ago). Ten-year risk for CV events according to the FRS was calculated as described by D'Agostino[24] and divided into three risk categories: low (<10%), intermediate (10-20%) and high (>20%), as recommended by Wilson.[25]

Cardiovascular events

Follow-up for the present investigation is defined as time between baseline urine collection and the date of a first cardiovacular event or 1 January 2009. The composite primary endpoint was defined as the combined incidence of CV mortality and CV morbidity after baseline screening. CV morbidity was defined as hospitalization with a primary discharge diagnosis of documented non-fatal myocardial infarction or myocardial ischemia, cerebrovascular accident and / or peripheral vascular disease. The date of admission was used as the date of the event. Data on mortality (including cause of death) were retrieved from Statistics Netherlands and coded according tot the 10th revision of the International Classification of Diseases.[26] Follow-up data on hospitalization for CV morbidity were derived from records held by PRISMANT, the Dutch national registry of hospital discharge diagnoses.[27]

Table 1 Baseline characteristics for all subjects and for subjects classified by quintiles of MR-proADM

Characteristics	Total	Quintiles of MR-proADM (nmol/l)					P-value (for trend)
		1	2	3	4	5	
	N = 7903	N = 1580	N = 1581	N = 1581	N = 1581	N = 1580	
MR-proADM (nmol/l), min-max		0.01-0.27	0.28-0.34	0.35-0.40	0.41-0.48	0.49-2.19	
MR-proADM (nmol/l)	0.39±0.14	0.21±0.05	0.31±0.02	0.38±0.02	0.44±0.02	0.59±0.12	<0.001
Age (yrs)	49±13	43±11	44±11	47±11	51±11	60±11	<0.001
Male Gender (%)	49.0	37.7	50.2	54.5	53.1	49.5	<0.001
Smoking / quit smoking <1yr (%)	38.0	33.0	36.2	39.4	41.4	40.3	<0.001
BMI (kg/m^2)	26.1±4.2	25.1±3.9	25.1±3.8	25.6±3.9	26.4±4.1	28.1±4.6	<0.001
Systolic BP (mmHg)	129±20	124±18	124±18	126±18	130±20	138±23	<0.001
Diastolic BP (mmHg)	74±10	72±9	72±9	73±9	75±10	77±10	<0.001
Heart rate (bpm)	69±10	69±10	68±10	69±10	70±10	70±11	<0.001
Myocardial infarction (%)	6.5	4.4	4.3	5.0	5.4	13.4	<0.001
Stroke (%)	0.8	0.6	0.3	0.4	1.1	1.8	<0.001
Hypertension (%)	30.9	20.7	21.4	23.7	34.8	54.2	<0.001
Hypercholesterolemia (%)	26.1	17.7	20.2	24.8	30.0	37.8	<0.001
Diabetes Mellitus (%)	3.6	1.7	1.7	2.3	3.9	8.6	<0.001
Glucose (mmol/l)	4.9±1.1	4.7±0.9	4.7±0.9	4.8±1.0	4.9±1.1	5.3±1.5	<0.001
Total cholesterol (mmol/l)	5.6±1.1	5.4±1.1	5.4±1.1	5.6±1.1	5.8±1.1	6.0±1.1	<0.001
HDL cholesterol (mmol/l)	1.33±0.40	1.40±0.41	1.35±0.40	1.33±0.41	1.30±0.40	1.25±0.37	<0.001
Triglycerides (mmol/l)	1.15 (0.84-1.68)	1.08 (0.78-1.53)	1.03 (0.76-1.51)	1.12 (0.82-1.62)	1.22 (0.87-1.71)	1.37 (1.02-1.94)	<0.001
C-reactive protein (mg/l)	1.3 (0.6-2.9)	1.0 (0.4-2.4)	0.9 (0.4-2.2)	1.0 (0.5-2.4)	1.3 (0.6-2.9)	2.3 (1.1-4.9)	<0.001
NT-proBNP (ng/l)	37 (17-73)	34 (16-62)	29 (13-55)	32 (14-59)	38 (17-75)	62 (31-128)	<0.001
UAE (mg/24h)	9.38 (6.37-17.05)	8.50 (6.09-13.78)	8.73 (6.19-14.67)	9.35 (6.39-15.69)	9.37 (6.43-17.38)	11.85 (6.94-27.84)	<0.001
Cystatin C (mg/l)	0.77 (0.69-0.87)	0.71 (0.64-0.80)	0.73 (0.68-0.83)	0.76 (0.68-0.83)	0.80 (0.72-0.88)	0.90 (0.80-1.03)	<0.001
eGFR (ml/min/1.73m^2)	81±15	84±15	85±14	83±13	80±13	71±14	<0.001

MR-proADM = mid-regional portion of pro-adrenomedullin; BMI=body mass index; BP=blood pressure; HDL cholesterol= high-density lipoprotein cholesterol; NT-proBNP=N-terminal pro-brain-type natriuretic peptide; UAE=urinary albumin excretion; eGFR=estimated glomerular filtration rate.

Statistical analysis

By design, the PREVEND study overselected subjects with an elevated UAE to acquire sufficient subjects with microalbuminuria. It should be clear that this is not a random sample of a general population, where all elementary units have an equal probability of being selected. Statistical formulas to calculate population parameter estimates should be used to account for the likelihood of selection. A design-based analysis was performed to overcome this overselection of subjects with elevated UAE. This statistical weighting method allows conclusions to be generalized to the general population.[28] P-values for trend were calculated between quintiles of MR-proADM. Because of skewed distribution, NT-proBNP, UAE, cystatin C, serum triglycerides and hs-CRP were transformed to their natural logarithms. Results are summarized as hazard (risk) ratios (HR) with 95% confidence intervals (CI). To assess which factors are most strongly associated with MR-proADM, we first performed univariate linear regression analyses, followed by multivariate backward linear regression analyses using bootstrapping (1000x, entry criterium 70%; default p-value for model entry <0.05, default p-value to remain in model <0.10). To avoid multi-colinearity in the latter analyses, we selected the strongest variable from strongly related domains (waist for the waist/bmi domain, systolic blood

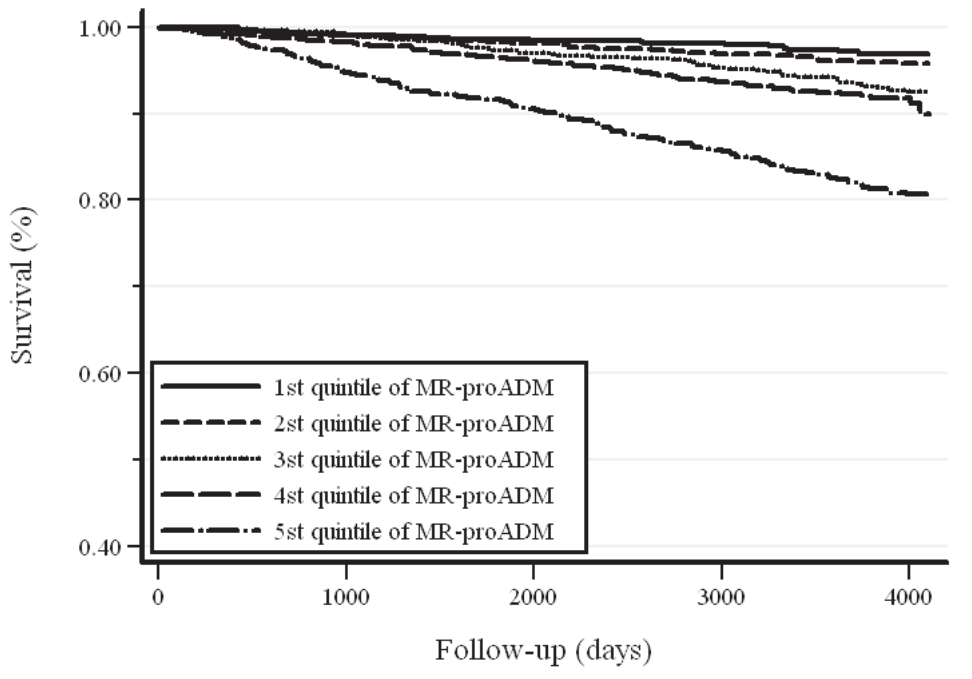

Figure 3 Time to first event by Kaplan-Meier estimates for MR-proADM on the primary endpoint.

Table 2 Univariate and multivariate analysis investigating associations between subject characteristics and MR-proADM levels

Univariate regression analysis				Multivariate regression analysis	
	Standardized coefficient	P	r^2	Standardized coefficient	P
Age (yrs)	0.44	<0.001	0.20	0.32	<0.001
Female Gender	-0.06	0.019	<0.01	-0.12	<0.001
Smoking / quit smoking <1yr	0.12	<0.001	<0.01	0.18	<0.001
BMI (kg/m^2)	0.26	<0.001	0.07	0.16	<0.001
Systolic BP (mmHg)	0.24	<0.001	0.06		
Diastolic BP (mmHg)	0.16	<0.001	0.03		
Heart rate (bpm)	0.05	<0.001	<0.01	0.03	0.014
Myocardial infarction	0.50	<0.001	0.01		
Cerebrovascular accident	0.52	0.008	<0.01		
Hypertension	0.53	<0.001	0.06		
Hypercholesterolemia	0.38	<0.001	0.03		
Diabetes Mellitus	0.76	<0.001	0.02	0.23	0.016
Glucose (mmol/l)	0.19	<0.001	0.03		
Total cholesterol (mmol/l)	0.17	<0.001	0.03		
HDL cholesterol (mmol/l)	-0.10	<0.001	0.01		
Triglycerides (mmol/l)	0.15	<0.001	0.02		
C-reactive protein (mg/l)	0.19	<0.001	0.04		
NT-proBNP (ng/l)	0.22	<0.001	0.05	0.12	<0.001
UAE (mg/24h)	0.15	<0.001	0.02		
Cystatin C (mg/l)	0.27	<0.001	0.09	0.15	<0.001
eGFR ($ml/min/ 1.73m^2$)	-0.31	<0.001	0.10		

Dependent factor: Mid-regional portion of pro-adrenomedullin (MR-proADM). BMI=body mass index; BP=blood pressure; HDL cholesterol=high-density lipoprotein cholesterol; NT-proBNP=N-terminal pro-B-type natriuretic peptide; UAE=urinary albumin excretion; eGFR=estimated glomerular filtration rate

pressure from the blood pressure/hypertension domain, cystatin C from renal domain). Kaplan-Meier estimates of the distribution of times from baseline to CV events were generated; log-rank tests were calculated to compare the survival curves between the groups. Multivariate Cox proportional hazards regression analysis was performed, with all significant parameters from the univariate analysis and other relevant covariates from previous studies. MR-proADM was entered linear and log-transformed, to assess best fit. We observed a significant statistical interaction between log-transformed MR-proADM and age with CV event outcome. Therefore, an interaction variable was added to the model and hazard ratios derived from this Cox proportional hazards model were plotted in a figure. Subjects were classified as young, middle-aged and old age (30, 50, 70 years respectively) to assess interpretation of clinical value. To assess the additive value of MR-proADM over the FRS, we evaluated the Intergrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) indices for MR-proADM (as a continuous variable) according to FRS (divided in risk categories). Subjects with a history of CV disease at baseline were excluded from the

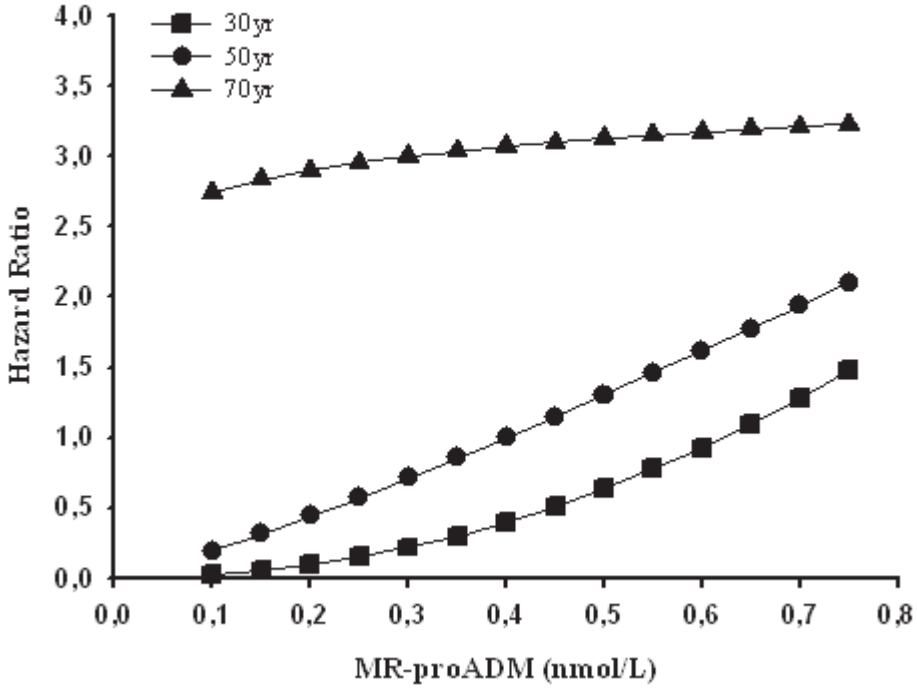

Figure 4 HRs of the mid-regional portion of pro-adrenomedullin (MR-proADM) on cardiovascular (CV) events (combined CV mortality and CV morbidity) by age. Reference HR is the mean MR-proADM and mean age in PREVEND.

analysis with the FRS. We evaluated the NRI in the entire population and in age strata because of the interaction with age. All reported probability values are two-tailed and P<0.05 was considered statistically significant. All analyses were performed using StataIC (version 11.0 software for Windows).

Results

The frequency distribution of MR-proADM is shown in Figure 2. The distribution appears normal with a few positive outliers and 90% of measurements below 0.55 nmol/l. Mean (SD) MR-proADM at baseline was 0.39 (±0.14) nmol/l, mean age was 49 (±13) years and 49% was of male sex. Baseline characteristics for all subjects and for subjects classified by quintiles of MR-proADM are summarized in Table 1. Compared to lower quintiles, individuals in higher quintiles were significantly older, had higher BMI, cholesterol and glucose levels, higher blood pressure and heart rate, and suffered more from CV disease at baseline (all P for trend <0.001). Hs-CRP, UAE, cystatin C and NT-proBNP levels were also significantly elevated in higher quintiles (all P for trend <0.001).

Table 3 Reclassification of participants without CV disease at baseline *

Framingham Risk Score	Model with Framingham Risk Score and MR-proADM			
	<10% risk	10-20% risk	>10% risk	Total no.
Participants with CV event				
<10% risk	152 (89.4)	18 10.6)	0 (0)	170
10-20% risk	9 (7.0)	97 (75.2)	23 (17.8)	129
>20% risk	0 (0)	13 (7.8)	153 (92.2)	166
Total no.	161	128	176	465
Participants with no CV event				
<10% risk	4826 (98.1)	95 (1.9)	0 (0)	4921
10-20% risk	138 (16.4)	659 (78.2)	46 (5.4)	843
>20% risk	0 (0)	71 (16.0)	372 (84.0)	443
Total no.	4964	825	418	6207

* Subjects with a history of CV disease at baseline were excluded for the analysis with the FRS. Data presented as number (percent). The Net Reclassification Improvement was estimated at 0.52 (P=0.003).

In univariate analysis, all investigated subject characteristics except HDL-cholesterol, eGFR and female gender, correlated positively with MR-proADM, with strongest associations for age (R^2=0.20), eGFR (R^2=0.10), cystatin C (R^2=0.09), waist circumference (R^2=0.09), NT-proBNP R^2=0.08), BMI (R^2=0.07), blood pressure (R^2=0.07) and hypertension (R^2=0.07) (Table 2). In a backward multivariate analysis, age, waist circumference, heart rate, NT-proBNP, cystatin C, smoking status and presence of diabetes mellitus remained significantly associated with MR-proADM (model R^2=0.28, Table 2). A total of 7,903 subjects were followed for a median of 10.5 years (IQR 9.9–10.8). The pre-specified primary endpoint occurred in 752 subjects (9.5%). The incidence of CV events increased with increasing quintiles of MR-proADM, from 8.0% in the bottom quintile (<0.21 nmol/l) to 44.4% in the top quintile (≥0.59nmol/l) (P<0.001 for trend). A Kaplan-Meier analysis of time to first CV event according to quintiles of MR-proADM is shown in Figure 3.

In total, 576 subjects (7.3%) died during follow-up, of whom 145 (25.2%) of CV causes. All cause mortality increased with increasing quintiles of MR-proADM, from 7.6% in the bottom quintile to 48.1% in the top quintile (P<0.001 for trend). The incidence of CV-related mortality also increased with higher levels of MR-proADM (P<0.001).

In Cox proportional hazard regression analyses, log-transformed MR-proADM was significantly associated with increased risk for CV events, in both crude models and models adjusted for Framingham CV risk factors (age,

gender, blood pressure, HDL cholesterol, diabetes mellitus and smoking) and other CV markers (NT-proBNP, hs-CRP and UAE). The latter was not the case for all-cause mortality. A significant interaction between MR-proADM and age was found for incident CV events (P=0.002). The adjusted increase in predicted hazard for CV risk with higher MR-proADM obtained from the Cox proportional hazard analysis is depicted against age in Figure 4. A subject with a mean age (50 years) and mean MR-proADm (0.39 nmol/l) was used as a referent. The figure shows that in older subjects (70 years), variation in MR-proADM levels is not associated with CV disease risk, unlike for middle-aged (50 years) and younger subjects (30 years). In a middle-aged subject, there is an almost linear relationship between MR-proADM and CV risk. In a younger subject, the relationship with CV risk increase is closer to exponential.

The Integrated Discrimination Improvent (IDI) index for the model (the same model used in the Cox proportional hazard regression analysis) including MR-proADM was significant: P=0.002 (outcome variable: CV mortality and morbidity). After excluding subjects with a previous CV history, the area under the curve (AUC) for the FRS in our population is 82% for predicting CV events. Adding MR-proADM to FRS improved the AUC by 0.5% (P<0.001; c-statistics). In the entire population, the NRI of MR-proADM over the FRS was nearly significant (P=0.08) and was mainly driven by correct reclassification to a lower risk category in 4% of subjects who did not have a CV event (P<0.001). Given the interaction between MR-proADM and age for CV risk, we repeated the NRI analysis in subjects ≤70yrs of age (N = 7,475). This resulted in reclassificaiton of 413 subjects (P=0.003) and we observed a significant up-reclassification in 41 subjects with a CV event (P=0.017), as well as a significant down-reclassification in 209 subjects without a CV event (P<0.001), see Table 3.

Discussion

This study describes the association between plasma MR-proADM and CV event risk and outcome in the general population. MR-proADM appears to be a strong independent predictor of CV events, in particular in younger subjects (≤70yrs), and adds to existing conventional and novel CV risk markers prediction models. The large PREVEND cohort, with almost 83,000 subject-years of follow-up, provides good opportunity for large-scale evaluation of this emerging biomarker and provides new insights into its association with CV disease.

Reliable quantification of ADM has been hampered by its short half-life, the immediate binding of ADM to receptors in the vicinity of its production site and technical difficulties.[9, 29] Limited general population data are available on the stable equivalent of ADM, MR-proADM. Smith et al. and Melander et al. measured MR-proADM in a general population cohort, finding mean (SD) MR-proADM levels of 0.42 (0.13)[10] and 0.46 (0.13),[30] respectively. Bhandari et al. examined hypertensive subjects and found much higher levels of MR-proADM, with a mean (SD) of 0.59 (0.18) in subjects without left ventricular hypertrophy (LVH) and 0.73 (0.25) in subjects with LVH.[16] In another study by Dieplinger et al., MR-proADM was assessed in a population with mild to moderate renal dysfunction and found higher levels of MR-proADM, increasing with worsening renal function,[7] from 0.43 to 1.34 nmol/l in subjects with eGFR >90 and <30. respectively. All studies - including ours - found a relatively normal distribution of MR-proADM, with only a small number of outliers at the high end of the distribution curve. The mean (SD) MR-proADM in our population was 0.39 (0.14), lower than in the studies mentioned above. This difference may be eplained by the fact the PREVEND cohort is comprised of relatively young subjects (mean age 49 years) with low prevalence of co-morbidities at baseline. In line with other studies, the strongest correlations were found with age and kidney function in both univariate and multivariate analyses. Waist circumference, BMI and blood pressure were also correlated with MR-proADM in our cohort, but in the multivariate model, only waist circumference remained significantly associated. MR-proADM may be most affected by ageing and kidney function, but may also be influenced by pressure and volume load, as reflected by the independent association with blood pressure and NT-proBNP.

In our cohort, we evaluated the association between MR-proADM and CV events, i.e. combined CV mortality and morbidity. The highest event rates were found in the higher range of plasma MR-proADM values (5th quintile: >0.59 nmol/l) compared with lower values. The incidence of CV events followed a logarithmic increase for higher values of MR-proADM, indicating that subjects with the highest levels of MR-proADM are most at risk for CV disease. This effect remained when adjusted for all relevant CV risk variables.

In crude, unadjusted models, the predictive value of MR-proADM for all-cause and CV mortality and CV morbidity is high. Interestingly, when adjusted for common variables such as the conventional CV risk factors (FRS) and several emerging CV risk factors, including hs-CRP and NT-proBNP, the predictive value of MR-proADM increases for CV events. MR-proADM was not an independent predictor for all-cause mortality after adjusting for the CV risk factors mentioned above. For CV mortality, the predictive value of MR-proADM on outcome did not reach statistical significance (P=0.33), but this may be due to lacking power, given the limited number of fatal CV events.

Survival analyses showed a significant interaction between MR-proADM with age for prediction of CV events, which is consistent with the strongest association with the primary endpoint in younger subjects. NRI analyses resulted in a significant reclassification in middle-aged and young subjects, with subjects with a CV event correctly reclassified into a higher risk category and event-free subjects into a lower risk category. This reclassification was not present in subjects >70yrs (P=0.32), suggesting added prognostic value for younger subjects in particular. The reason for this interaction with age remains unknown. A possible explanation may be that in older subjects, upregulation of ADM is at the end of its dose-effect relationship, while correlation with outcome is visible primarily in early, subclinical stages of CV disease. CV risk stratification using biomarkers can help identify subjects in the community who may benefit most from preventive therapeutic intervention. In populations with low to intermediate risk for CV disease, data on the additive value of established and / or novel biomarkers is conflicting. Our results are in agreement with previous publications regarding the prognostic performance of MR-proADM. Most data were obtained in different cohorts with co-morbidities,[11-13,15] but also in the community.[30] Our results provide valuable knowledge about MR-proADM as an effective predictive biomarker for future CV events in younger subjects without other co-morbidities or history of CV disease. Whether specific preventive strategies or treatment may be of benefit for subjects with increased MR-proADM remains to be addressed before this biomarker can be used for routine screening.

Conclusion

This study gives a detailed overview of the distribution of MR-proADM in the general population and provides evidence for the value of MR-proADM as a potent and interesting biomarker for predicting CV events. We postulate that MR-proADM may be particularly valuable as a biomarker in younger subjects.

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Disclosures

JS is employed by BRAHMS GmbH / ThermoFisher Scientific, a company which manufactures and holds patent rights on the MR-proADM assay.

Statement Of Competing Interest

Nothing to declare

Contributorship Statement

All co-authors have contributed significantly to the manuscript, regarding interpretation of the data and revising it for important intellectual content.

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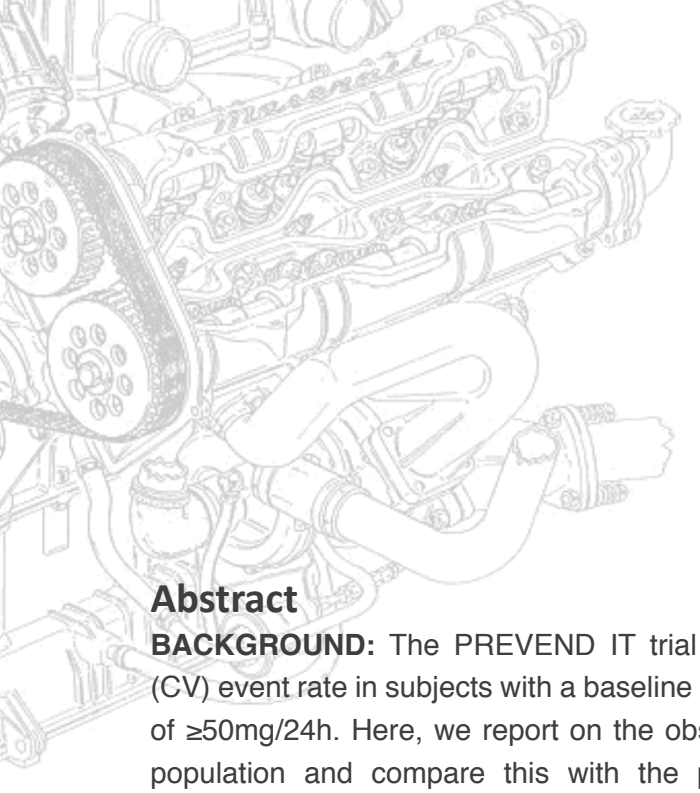

Abstract

BACKGROUND: The PREVEND IT trial reported on a high cardiovascular (CV) event rate in subjects with a baseline urinary albumin excretion (UAE) rate of ≥50mg/24h. Here, we report on the observed ten-year CV outcome of this population and compare this with the predicted Framingham Risk Score (FRS). In addition, we evaluated the effect of four years of fosinopril treatment on this relation.

METHODS AND RESULTS: From the PREVEND IT cohort, 833 subjects without history of CV disease, randomized to fosinopril (N = 412) or placebo (N = 421), were studied. The primary endpoint included CV mortality and adjudicated hospitalization for CV disease during a ten-year follow-up period. Mean age was 51±12 years and 65% were males, while prevalence of diabetes (2.6%) and use of CV drugs (3.5%) was low. Subjects were categorized to high UAE (≥50mg/24h) or low UAE (<50mg/24h). After ten years of follow-up, the event rate in the high UAE group was almost twice as high as predicted by the FRS (29.5% vs. 17.2%). Treatment for four years with fosinopril reduced the event rate to comparable levels of that predicted by FRS. The addition of UAE ≥50mg/24h to the FRS improved the Integrated Discrimination Improvement (P=0.033) and increased the area under the curve by 0.54% (P=0.024).

CONCLUSIONS: The ten-year CV risk of subjects with an elevated UAE (≥50mg/24h) is substantially underestimated by the FRS. Treatment with fosinopril successfully reduced this increased event rate to FRS-predicted CV risk.

Chapter 8

Elevated urinary albumin excretion complements the framingham risk score for prediction of cardiovascular risk: response to treatment in PREVEND IT

Frank P. Brouwers
Folkert W. Asselbergs
Hans L. Hillege
Ron T. Gansevoort
Rudolf A. de Boer
Wiek H. van Gilst

Submitted

Background

Cardiovascular (CV) disease may be predicted by a variety of clinical, biochemical, and surrogate risk factors. Of these, endothelial dysfunction has also been linked to the development of atherogenesis.[1, 2] Increased levels of urinary albumin excretion (UAE) do not only provide an indication of early renal dysfunction, but functions also as a marker of endothelial dysfunction.[3] Many trials have reported on a high prevalence of elevated UAE in high risk subjects suffering from diabetes,[4, 5] renal failure,[6] heart failure,[7, 8] but also in subjects from the general population.[9] An increased UAE was in every cohort associated with worse outcome. Recently, the Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) confirmed these results and reported on a CV event rate of almost 30% in subjects with a baseline UAE ≥50mg/24h after 10 years of follow-up.[10] Some have proposed that UAE may be a useful surrogate marker for CV disease. It is unclear whether conventional CV risk prediction models, like the Framingham Risk Score (FRS) can be used in a population with albuminuria.[11, 12] In addition, it remains unclear whether addition of UAE could significantly improve prognostic performance of the FRS. In this analysis, we retrospectively investigate the quality of the CV risk estimations by the FRS by comparing it to the observed outcome in PREVEND IT.

Material and methods

Study population

The study was performed using data of the PREVEND IT study, which has been described elsewhere.[10, 13] Briefly, the aim of PREVEND IT was to assess the value of albuminuria as an indicator of increased CV risk in the general population. The key entry criteria of the PREVEND IT were persistent microalbuminuria (one urinary albumin concentration ≥10 mg/l in an early morning spot urine test and at least one 15 to 300 mg/24h in two 24h urine samples), absence of antihypertensive and lipid-lowering medication, a blood pressure of <160/100 mmHg and total cholesterol of <8.0 mmol/l or <5.0 mmol/l in the case of previous myocardial infarction. From April 1998 to June 1999, 864 subjects were included in the PREVEND IT and were randomized to 20mg fosinopril or matching placebo for the duration of four years (referred to as “active trial period”). At the end of this four year period, all subjects were taken off study medication and returned to the care of their general practitioners. Follow-up time was extended for an additional 6.0 years after the active trial period was ended, resulting in a total follow-up time

of 10.0 years. To evaluate the FRS in our population, we excluded subjects in which variables of FRS were missing (N = 2, both missing values of HDL cholesterol) or subjects with a history of CV disease (N = 29). Finally, a total of 833 subjects were eligible for the current analysis. An independent data and safety monitoring committee regularly monitored the progress of PREVEND IT during the entire follow-up period. The study was approved by the institutional medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all subjects before randomization.

Endpoint collection and follow-up

The composite primary endpoint is the combined incidence of CV mortality and hospitalization for CV morbidity. CV morbidity was defined as hospitalization for documented non-fatal myocardial infarction or myocardial ischemia, heart failure, peripheral artery disease, and / or cerebrovascular accident. These endpoints are the same as for the FRS for general CV disease.[14] Follow-up for all surviving subjects after the active trial was collected via personal communication and electronic hospital files. Data on mortality were retrieved from the municipal register. Cause of death was obtained through the Dutch Central Bureau of Statistics and was coded according to the 10th revision of the International Classification of Diseases. Follow-up on hospitalization for CV morbidity was derived from records held by PRISMANT, the Dutch national registry of hospital discharge diagnoses.[15] In addition, personal communication was used to obtain data from subjects lost to follow-up. The date of admission was used as the date of the event. Details of each CV event were obtained from the treating physician. The independent endpoint committee of the active trial period reviewed all endpoints and the members had no knowledge of subject's treatment assignments.

Measurements

At trial follow-up visits, various clinical and biochemical measurements were performed and two 24h urine collections were obtained. Systolic and diastolic blood pressures were calculated as the mean of the last two of ten consecutive measurements, using an automatic Dinamap XL model 9300 series device (Johnson & Johnson Medical Inc). Serum creatinine, plasma cholesterol and glucose were determined in one laboratory by Kodak Ektachem dry chemistry

(Eastman Kodak, Rochester, NY, USA), using an automated enzymatic method. The intra- and interassay variation coefficient of serum creatinine were respectively 0.9% and 1.1%. Serum triglycerides were measured enzymatically. A commercially available assay system was used to assess high-density lipoprotein (HDL) cholesterol (Abbott Inc., Abbott Park, IL, USA). Urinary albumin concentrations were determined by nephelometry with a threshold of 2.3 mg/l and intra-assay and interassay coefficients of variation of less than 2.2% and 2.6%, respectively (Dade Behring Diagnostic). Ten-year risk for CV events according to the FRS was calculated as described by D'Agostino[14] and divided into three risk categories: low (<10%), intermediate (10-20%) and high (>20%), as recommended by Wilson.[16] UAE was categorized by low (<50 mg/24h) vs. high (≥50 mg/24h), according to the quintiles used in PREVEND IT.[10, 13]

Statistical analysis

Baseline continuous data are reported as mean (standard deviation) for normal data. UAE and triglycerides showed a log-linear functional shape with the response variable and were transformed to a 2-log scale and reported as median (interquartile range). This means that risk estimates should be interpreted as the relative risk of values were doubled (e.g. 1 to 2 mg/l or 10 to 20 mg/24h). Times to first occurrence of outcomes are presented as Kaplan-Meier estimates, and statistical differences between placebo and active treatment were analyzed by log-rank testing. To assess the additive value of UAE over the FRS, we evaluated the Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI) indices for UAE (both as a continuous variable as well as dichotomized to high vs. low, using a cut-off of 50mg/24h) according to FRS. All reported probability values are two-tailed and $P<0.05$ was considered as the nominal level of statistical significance. All analyses were performed using StataIC (version 11.0 software for Windows).

Results

Baseline characteristics of subjects divided by low (<50 mg/24h) vs. high UAE (≥50 mg/24h) are summarized in Table 1. These characteristics show a middle-aged population with a low prevalence of conventional CV risk factors, exemplified e.g. by a low prevalence of diabetes mellitus (4.0%), and little use of CV drugs (3.5%). Subjects in the high UAE group were at baseline older and had higher levels of systolic and diastolic blood pressure and a higher resting heart rate. Also, levels of glucose,

triglycerides and serum creatinine were slightly increased in the high UAE group. Baseline median FRS was 12.7% and was different between UAE groups, namely 11.9% (IQR 5.2-23.9) and 17.1% (IQR 7.8-30.7) for respectively the low UAE and the high UAE group (P=0.001). Mean follow-up was 10.0 years (range 9.8 to 10.3) from start of active trial until 1 January 2009.

At baseline, median UAE was 19 mg/24h (IQR 15-29) in the low UAE group and 77 mg/24h (IQR 59-115) for the high UAE group (P<0.001). The following changes, during the entire follow-up period are depicted in Figure 1. The low and high groups of UAE are divided by treatment group. In the low UAE group, four years of treatment with fosinopril during active trial resulted in a decrease in median UAE from 20 mg/24h to 15 mg/24h (P=0.003 compared to baseline). In the high UAE group, fosinopril treatment decreased UAE to 55 mg/24h (P=0.003 compared to baseline). Three months after cessation of fosinopril, median UAE increased in both groups and remained stable during further follow-up. UAE was unaffected by placebo during the entire follow-up period.

During the entire follow-up, the primary endpoint occurred in 119 subjects. The event rate in the high UAE group was significantly higher, compared to the low UAE group (22.0% vs. 12.3%, respectively, P=0.001). Treatment with fosinopril lowered the event rate in the high UAE group to the same height as

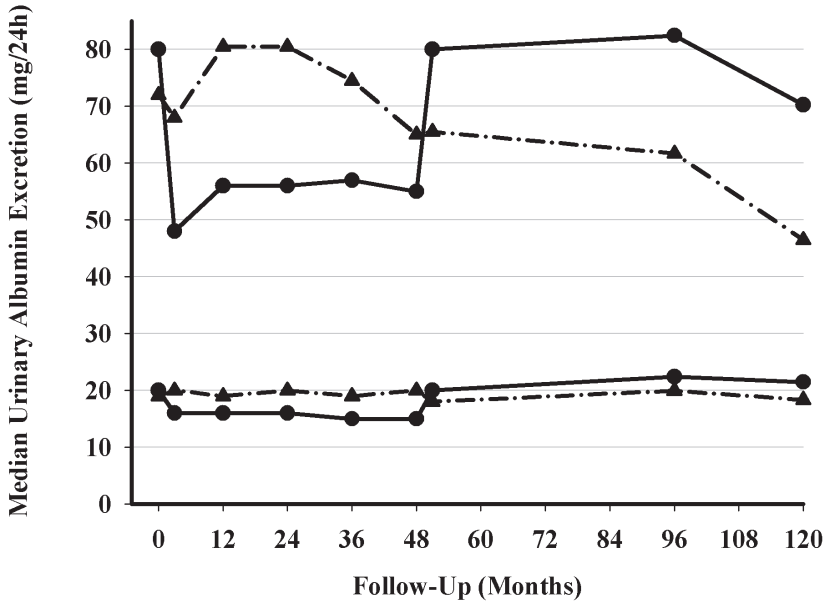

Figure 1 Median urinary albumin excretion (mg/24h) by treatment and visit

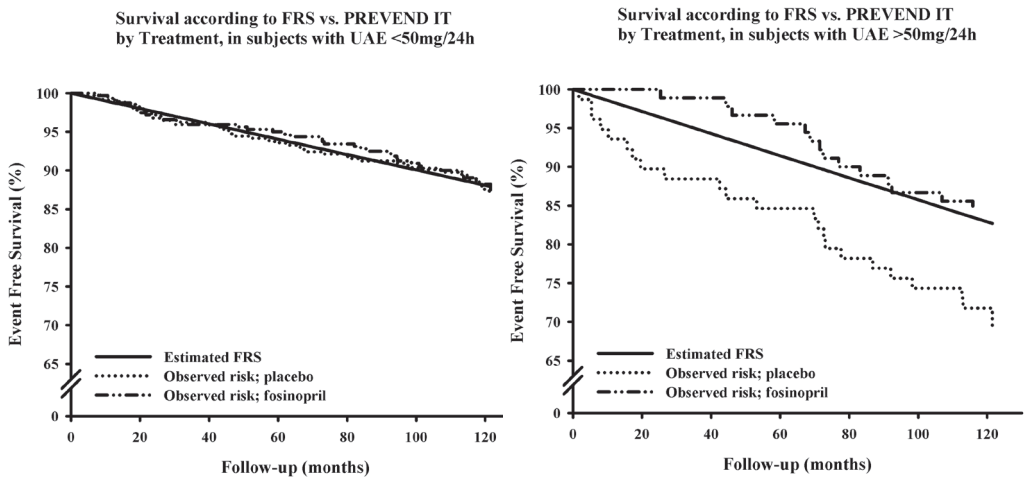

Figure 2A and 2B Predicted Framingham Risk Score compared to Kaplan-Meier estimates of incidence of cardiovascular events in fosinopril and placebo group, divided by a UAE <50mg/24h and UAE ≥50mg/24h

subjects with low UAE levels at start (15.6% vs. 12.3%, respectively, P=0.436). The observed ten-year event rate for both the low UAE group as well as the high UAE group is plotted against the FRS-predicted risk, in Figure 2A and 2B. In subjects with UAE <50mg/24h, the observed event rate is identical to the FRS-predicted event rate. There was no effect of fosinopril on the observed event rate in the low UAE group. In contrast, the ten-year event rate of subjects in the group UAE ≥50mg/24h is significantly underestimated compared to the predicted ten-year FRS-predicted risk. The event rate almost doubled, from 17.2% (FRS-predicted) to 29.5 (observed). Treatment for four years with fosinopril during the active trial period significantly reduced observed CV risk and outcome to compared with placebo, and normalized the actual CV risk to the FRS-predicted CV risk level.

The Integrated Discrimination Improvement (IDI) index for including UAE to the FRS was significant, P=0.033 (outcome variable: primary endpoint). The area under the curve for the FRS in our population is 76% for predicting CV events. Adding UAE to FRS improved the area under the curve by 0.54% (P=0.036; c-statistics). In the entire population, the NRI of UAE over the FRS was not significant (P=0.313). Given the increased event rate observed in subjects with UAE ≥50mg/24h, we repeated the NRI analysis in subjects in the high UAE group (N = 167). This resulted in a reclassification of 4.6%, however not significant (P=0.313), see supplementary Table 1A and 1B.

Table 1 Baseline characteristics of PREVEND IT subjects with high vs. low UAE (N = 833)

	Urinary Albumin Excretion		
Variables	Low (<50mg/24h) (N = 665)	High (≥50mg/24h) (N = 168)	P-value
Age (yrs)	50±12	54±12	<0.001
Males (%)	65.0	64.9	0.984
Caucasian (%)	96.2	95.8	0.575
Body mass index (kg/m^2)	26±4	27±5	0.009
Obesity (>30kg/m^2)	13.9	17.3	0.263
Smoking (%)	39.6	40.5	0.826
Systolic blood pressure (mmHg)	128±17	135±19	<0.001
Diastolic blood pressure (mmHg)	75±10	78±10	<0.001
Heart rate (bpm)	69±10	71±11	0.034
Cholesterol (mmol/l)			
Total	5.8±1.0	5.8±1.1	0.992
HDL	1.0±0.3	1.0±0.3	0.641
LDL	4.1±0.9	4.0±1.0	0.519
Triglycerides (mmol/l)	1.3 (0.9-1.9)	1.5 (1.0-2.1)	0.001
Glucose (mmol/l)	5.1±1.2	5.2±1.3	0.116
eGFR (kg/min/1.73m^2)	83±14	79±15	0.001
Serum creatinine (μmol/l)	83 (75-92)	86 (76-96)	0.034
UAE (mg/24h)	19.0 (14.0-28.0)	77.0 (59.5-124.5)	<0.001
Diabetes Mellitus (%)	2.4	3.6	0.400
Prior event (%)	0.0	0.0	NA
Cardiovascular drugs (%)	3.0	5.4	0.138
Aspirin and antiplatelet agents	1.1	1.8	0.101
Beta-Blockers	0.6	0.6	0.993
Nitrates	0.0	0.0	NA
Diuretics	0.3	1.8	0.026
Calcium channel blockers	0.8	0.6	0.830
Digoxin	0.6	1.8	0.133
Framingham Risk Score	11.9 (5.2-23.9)	17.1 (7.8-30.7)	0.001

UAE Urinary albumin excretion; HDL High-density lipoprotein; LDL low-density lipoprotein; eGFR estimated glomerular filtration rate; NA not available

Table 2 Observed incidence of primary endpoint, divided by UAE groups

	UAE <50mg/24h			UAE ≥50mg/24h		
Mortality	Placebo (N = 343)	Fosinopril (N = 322)	P	Placebo (N = 78)	Fosinopril (N = 90)	P
All causes	19 (5.5)	23 (7.1)	0.396	10 (12.8)	8 (8.9)	0.411
CV causes	7 (2.0)	6 (1.9)	0.869	4 (5.1)	1 (1.1)	0.126
Hospitalization for						
Non-fatal MI	21 (6.1)	22 (6.8)	0.710	9 (11.5)	9 (10.0)	0.748
Heart failure	4 (1.2)	6 (1.9)	0.460	4 (5.1)	3 (3.3)	0.561
PVD	5 (1.5)	5 (1.6)	0.920	3 (3.9)	1 (1.1)	0.246
CVA	12 (3.5)	7 (2.2)	0.306	6 (7.7)	2 (2.2)	0.097
Total CV morbidity	39 (11.4)	38 (118)	0.862	22 (28.2)	13 (14.4)	0.029
Primary endpoint	42 (12.2)	40 (12.4)	0.945	23 (29.5)	14 (15.6)	0.030

Values are N(%) UAE urinary albumin excretion; CV cardiovascular; MI myocardial infarction; PVD peripheral vascular disease; CVA cerebrovascular disease

Discussion

Previously, the PREVEND IT trial reported on a high CV risk in subjects with elevated UAE (≥50mg/24h), with an event rate of almost 30% after ten years of follow-up.[10] In this sub-analysis we compared the observed event rate in PREVEND IT with the populations' FRS-estimated risk. Our results indicate that the FRS substantially underestimates CV risk of subjects with UAE ≥50mg/24h and that this increased risk is amenable to treatment with the ACE-inhibitor fosinopril, the use of which reduced the risk to the FRS-estimated risk. Adding UAE to the FRS, using a cut point of 50mg/24h, furthermore increased the area under the curve and IDI in risk estimation.

The FRS is the most well-known and most widely used models for CV risk stratification. Although the FRS does not suffice for specific risk groups, for example young or low-risk patients,[17] its use for a general risk prediction for CV disease is undisputed. Still, multiple attempts have been made to improve CV risk stratification by adding variables to the FRS, like non-invasive vascular assessments,[18] coronary artery calcium score,[19] or brachial artery flow-mediated dilation,[20] and several other variables. Limited studies have been done investigating the additional value of UAE on the FRS. The group of Cao showed in elderly subjects that the combination of UAE with the FRS improved risk stratification, over a follow-up period of 5.6 years.[11] Other studies used albumin-creatinine ratio alone, or in

combination with other biomarkers to improve FRS.[21, 22]

In the current analysis, we compared the predicted ten-year CV risk to the observed event rate during follow-up. For subjects with an UAE <50mg/24h, the FRS proved to be very accurate. In contrast, subjects in the highest UAE quintile (≥50mg/24h) were substantially underestimated with regard to their CV risk. The addition of UAE ≥50mg/24h to the FRS increased the IDI and area under the curve significantly, implying additional value in predicting individual ten-year CV risk. This is strengthened by the observed high incidence of CV events in subjects in the highest quintile of UAE. In addition, the increased rate of observed CV events was neutralized in the group treated with fosinopril. Fosinopril-treated subjects also showed a significant decrease in UAE during the active trial period, while there was little effect of fosinopril treatment on blood pressure.[13] We did however not find any additional value of UAE over the FRS using NRI, which can be explained by several factors. The IDI differs from the NRI in that the population is not cross-classified by fixed levels from the two prediction models. The conventional and widely used risk categories used in this analysis (≤10%; 11-20%; >20%) might not have been suitable for assessing additional value of UAE. Also, the baseline average FRS for subjects in PREVEND IT is 12.7%, which is already considerably increased. This is due to the relative high percentage of tobacco users and an average systolic blood pressure of 129mmHg at baseline in PREVEND IT. The lack of additional value of UAE might be caused by the already present high baseline risk for CV disease. Finally, the NRI was performed in the total population and the sub-group of subjects with UAE ≥50mg/24h, however irrespective of treatment group. This could have diluted the additional value of UAE, while subjects treated with fosinopril compared to placebo had less CV events during follow-up. Our study was unfortunately underpowered to assess the difference in added value of UAE over FRS for both treatment groups separately.

Limitations

The sample size of PREVEND IT does not allow making definite statements about the role of UAE in prediction CV risk.

Conclusions

In subjects with elevated UAE (≥50mg/24h) the actual ten-year CV risk was significantly higher than predicted by FRS, and this excess risk was neutralized by fosinopril treatment. The FRS should be used carefully in subjects with increased levels of UAE, as it underestimates their CV risk.

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Disclosures

None declared

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Supplementary eTable 1A Reclassification of participants without CV disease at baseline in the entire PREVEND IT population *

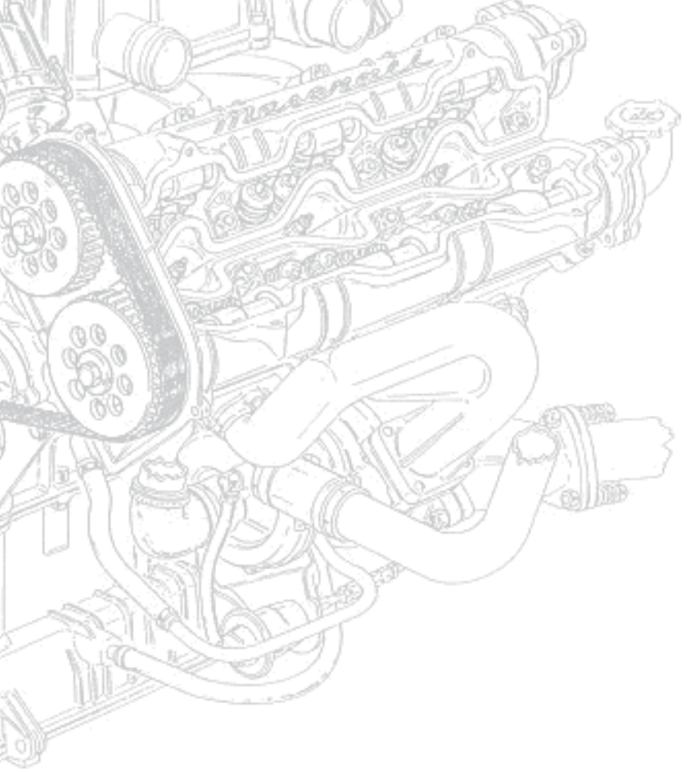
Framingham Risk Score	Model with Framingham Risk Score and UAE			
Participants with CV event	≤10% risk	11-20% risk	>20% risk	Total no.
≤10% risk	17 (94.4)	1 (5.6)	0 (0.0)	18
11-20% risk	6 (18.8)	23 (71.9)	3 (9.3)	32
>20% risk	0 (0.0)	4 (6.3)	60 (93.7)	64
Total no.	23	28	63	114
Participants with no CV event				
≤10% risk	370 (95.6)	17 (4.4)	0 (0.0)	387
11-20% risk	21 (12.3)	130 (76.5)	19 (11.2)	170
>20% risk	0 (0.0)	27 (18.1)	122 (81.9)	149
Total no.	391	174	141	706

* Data presented as number (percent). The NRI was estimated at -0.036 (P = 0.313)

Supplementary eTable 1B Reclassification of participants without CV disease at baseline in the PREVEND IT population UAE≥50mg/24h*

Framingham Risk Score	Model with Framingham Risk Score and UAE			
Participants with CV event	≤10% risk	11-20% risk	>20% risk	Total no.
≤10% risk	3 (75.0)	1 (25.0)	0 (0.0)	4
11-20% risk	0 (0.0)	5 (83.3)	1 (16.7)	6
>20% risk	0 (0.0)	0 (0.0)	27 (100.0)	27
Total no.	3	6	28	37
Participants with no CV event				
≤10% risk	52 (92.9)	4 (7.1)	0 (0.0)	56
11-20% risk	1 (4.0)	22 (88.0)	2 (8.0)	25
>20% risk	0 (0.0)	4 (8.2)	45 (91.8)	49
Total no.	53	30	47	130

* Data presented as number (percent). The NRI was estimated at 0.046 (P = 0.313)



Summary and future perspectives

In this thesis, the origin and manifestation of new onset heart failure are discussed with a special focus on clinical and pathophysiological differences between heart failure with reduced ejection faction (HFrEF) and heart failure with preserved ejection faction (HFpEF).

The first part of this thesis concerns the epidemiology of new onset heart failure, as well as clinical characteristics and biomarkers of new onset HFrEF and HFpEF. In **chapter 1** and **chapter 2**, an update is provided on incidence and prevalence of heart failure. During the past decade, several large, community-based, prospective studies have presented important epidemiological data on new onset heart failure. The available evidence suggests an overall decrease in heart failure incidence and successful preventive strategies for the development of heart failure. However, it should be noted that changes in HFrEF incidence may account for most of this decrease, while the incidence of HFpEF may have increased. These epidemiologic trends underscore the necessity to differentiate between patients with HFpEF and HFrEF. Earlier studies suggested that HFrEF and HFpEF might be two different cardiovascular syndromes and would require a different approach. However, our review showed that very few cohorts obtained factual information on left ventricular ejection fraction (LVEF) to discern HFrEF from HFpEF. Distinct risk factors in community-based cohorts are therefore not properly defined and studies directly comparing new onset HFrEF vs. HFpEF are lacking. Accordingly, **chapter 3** presents the incidence and epidemiology of new onset HFrEF and HFpEF in the large community-based Prevention of REnal and Vascular ENdstage Disease (PREVEND) cohort in The Netherlands. In total, 374 subjects were diagnosed with new onset heart failure during a 12-year follow-up period. HFrEF and HFpEF were classified by an adjudication committee based on LVEF and various other parameters (derived from ESC guidelines) at the time of diagnosis. The observed incidence rate of new onset heart failure in the PREVEND population was in agreement with previous epidemiologic studies in community-based cohorts. The proportion of patients with new onset HFpEF, compared to new onset HFrEF, was initially relatively low (34% vs. 66%, respectively), but there was a catch-up effect later on in the study, suggesting higher incidence of HFpEF in elderly subjects. Also, clear evidence is provided for a differential risk profile for HFpEF compared to HFrEF. It appears that substantial clinical differences arise years before signs and symptoms due to either HFrEF or HFpEF become apparent. Apart from higher age

and female sex, increased urinary albumin excretion, atrial fibrillation and renal dysfunction emerged as novel risk indicators for HFpEF. In **chapter 4**, these clinical differences between HFrEF and HFpEF are further amplified by evaluating the prognostic value of multiple biomarkers for both subtypes of heart failure. An increased risk for heart failure was observed for several biomarkers, and in particular for HFrEF. In contrast, there was no clinically relevant association of biomarkers with new onset HFpEF. Additionally, the incremental value per biomarker increased when the general population was categorized into low and high-risk subjects. This simple stratification was based on the presence or absence of previous cardiovascular disease at baseline of PREVEND. This investigation also included a biomarker score, in which the risk for new onset heart failure increased more than seven-fold for the combination of an increase in NT-proBNP, hs-TnT and urinary albumin excretion. Finally, in **chapter 5**, the best combination of common clinical and biochemical parameters was evaluated to establish the first risk prediction model for early identification of subjects at risk for new onset HFrEF and HFpEF. The risk model for heart failure included 21 commonly available variables and showed good internal validation and calibration. However, the predictive power for both heart failure syndromes was modest and therefore its clinical utility remains questionable. For HFpEF in particular, risk prediction will remain a significant challenge in daily clinical practice.

In the second part of this thesis, the aforementioned results are supported by several separate analyses, associating the prognostic value of single biomarkers with poor cardiovascular outcome. Urinary albumin excretion in particular has a powerful prognostic association with adverse cardiovascular outcome, as shown from data from the extended PREVEND Intervention Trial (PREVEND IT). The PREVEND IT was a randomized clinical trial with a 2x2 design, where subjects were randomized to 20mg fosinopril or matching placebo, and to 40mg pravastatin or matching placebo. In **chapter 6**, its follow-up was extended to ten years and it was evident that elevated urinary albumin excretion was associated with a significant increase in cardiovascular mortality and morbidity, especially in subjects in the highest quintile of albuminuria (≥50mg/24h). Additionally, the beneficial effects of fosinopril in reducing cardiovascular risk persisted after cessation of treatment during prolonged 'passive' follow-up. In **chapter 8**, a sub-analysis of PREVEND IT, the Framingham Risk Score was shown to substantially underestimate the ten-year

predicted risk for cardiovascular disease in these same subjects in the highest quintile of albuminuria (≥50mg/24h). Finally, **chapter 7** presents the results of the novel biomarker mid-regional pro-adrenomedullin. This multifunctional peptide is expressed primarily in endothelial cells, and is capable of promoting vasorelaxation, natriuresis, diuresis and cardiac output. This biomarker is associated with adverse cardiovascular outcome, especially in subjects below 70 years of age.

Discussion

Epidemiology

Heart failure is a major public health problem, with a prevalence of over 6.5 million in Europe and over 26 million worldwide.[1, 2] It is estimated that one in five adults over the age of 40 will develop heart failure in their lifetime, and as such, heart failure has repeatedly been identified as an emerging epidemic.[3, 4] The increase in the global prevalence of heart failure over the last few decades can be attributed to several factors: an aging population, an increase in the incidence of cardiovascular disease, improved treatment of heart disease in general (especially acute coronary syndromes), which all lead to a reduction in short-term mortality and heart failure development over time. Greater awareness of this heart failure epidemic and the fact that more reliable and sensitive diagnostic tools are available, e.g. natriuretic peptides and echocardiography, could also explain a disproportionate increase in the incidence and prevalence of heart failure. Despite the reported increase in prevalence, the majority of evidence indicates a stabilizing incidence of heart failure, and possibly even a decrease in some groups.[5-7]

The left ventricular ejection fraction (LVEF) enables classification of heart failure as preserved (HFpEF) or reduced (HFrEF).[8, 9] Although different cut-off values for LVEF have been proposed, general consensus is that heart failure with LVEF above 50% is considered preserved. It is estimated that the LVEF is preserved in approximately half of all heart failure cases in the community.[10-12] Epidemiologic data on the incidence and prevalence of heart failure according to ejection fraction and its development over time are limited. The available evidence suggests the current prevalence of HFpEF is increasing, in contrast to HFrEF.[13, 14] Another recent large study, including data from 275 hospitals in the USA, confirms these findings.[15] Importantly, in this thesis we suggest that this rise in number of HFpEF patients remains an underestimation of

the true burden of HFpEF. Clinical under-recognition of HFpEF may play a role, because signs and symptoms tend to be less specific and concomitant co-morbidities more common.[14, 16] Furthermore, studies on incidence and prevalence of heart failure comprised of hospitalized subjects, while few included outpatient data.[17-19] Again, this is especially true for HFpEF, which a significant proportion of stable outpatients with unexplained dyspnea may suffer from.[20]

Our attention is, or at least should be, shifting from HFrEF towards HFpEF. A significant development, as various studies published in recent years have shown that prognosis is equally poor for HFpEF and HFrEF.[16, 21] At the beginning of the 20th century, survival estimates after diagnosis of heart failure were 50% and 10% at 5 and 10 years, respectively.[22-24] Although there have been several studies reporting improved survival in the past decade, survival after heart failure diagnosis remains poor.[6, 25-27] These trends are in agreement with temporal major changes in the treatment of heart failure, and thus suggest that heart failure treatment is effective in the community. However, much progress remains to be accomplished. As the proportion of HFpEF, for which there is no specific treatment, is increasing over time, its prevalence will likely increase, underscoring the urgent need for new therapeutic approaches to this entity.

Differential characteristics of HFrEF and HFpEF

It has been speculated that HFrEF and HFpEF either represent distinct forms of heart failure, or exist as part of one heart failure spectrum.[9] Recent structural, functional and molecular biological arguments support the theory that they are two discrete disease processes.[28-31] This thesis provides further evidence that new onset HFrEF and HFpEF are different syndromes and that each require a different approach. Most data on HFrEF and HFpEF are derived from prevalent heart failure studies, where several retrospective cohort studies have shown clinical differences between patients with prevalent HFpEF and HFrEF. At first presentation, patients with HFpEF are older and more often female and obese than those with HFrEF. Furthermore, they are less likely to have coronary heart disease and more likely to have hypertension and atrial fibrillation.[12] On the other hand, patients with HFrEF are more likely to have a history of ischemic heart disease, defined as either prior myocardial infarction or ECG abnormalities.[11, 12, 32] Other risk factors which have been associated with HFrEF are diabetes mellitus and a history of alcohol abuse.[33, 34] Renal dysfunction is also a frequently occurring condition in both HFrEF and HFpEF,

the so-called cardiorenal syndrome.[35] Our data suggest, however, that renal dysfunction is a more significant risk factor for new onset HFpEF than for new onset HFrEF, based on measuring cystatin C or urinary albumin excretion.[36, 37]

We found similar differential clinical characteristics for HFrEF and HFpEF in PREVEND. Notably, distinct clusters of antecedent risk factors can be used to classify subjects at risk for new onset HFpEF vs. HFrEF. As such, our findings may have important implications for targeted heart failure prevention strategies. This is further strengthened by the observed mean time from baseline assessment to diagnosis of heart failure, which was 7.2 years. Additionally, time to diagnosis of HFpEF (8.3 years) was significantly longer than for HFrEF (6.6 years). The existence of the aforementioned different risk profiles for HFrEF and HFpEF, many years before symptoms of heart failure becomes manifest, probably reflects the long-term process of left ventricular remodeling preceding heart failure symptoms. Especially for asymptomatic individuals with hypertension, more aggressive antihypertensive treatment to prevent further left ventricular remodeling, leading to HFpEF, is recommended. Many specific risk factors for HFpEF are related to hypertensive end organ damage, such as atrial fibrillation, left ventricular hypertrophy and renal dysfunction – either functional damage, as reflected by cystatin C, or structural damage, as reflected by urinary albumin excretion.[36] For HFrEF, a similar strategy has already proven effective, as post-myocardial infarction anti-remodeling therapy significantly reduces the development of heart failure. While heart failure is epidemiologically still considered a disease of the elderly, the process of left ventricular remodeling begins many years earlier. Whether earlier and more aggressive treatment of cardiovascular risk factors for HFrEF and HFpEF should be a key strategy for preventing future new onset heart failure remains unclear.

Biomarkers

The question remains whether biomarkers can aid in early risk identification for new onset heart failure, as described above. The presence or absence of specific biomarkers represent separate pathophysiological pathways involved in the development of heart failure, and include enzymes, biologic substances, and markers of cardiac stress or myocyte injury.[38] Multiple biomarkers are currently available, reflecting several pathophysiological processes influencing the development of heart failure. Several established biomarkers exist in current heart failure diagnosis and management, however the only biomarkers

mentioned in current heart failure guidelines are NT-proBNP and hs-TnT.[4] The association of many new, emerging biomarkers with cardiovascular disease has yet to be determined, for example adrenomedullin, galectin-3, and the neurohormonal biomarkers renin and aldosterone. In this thesis, the predictive value of biomarkers for new onset heart failure was found to be modest. In other words, with regard to clinical utility, the additional value per biomarker was low. This is consistent with previous reports on the long-term predictive value of biomarkers for cardiovascular disease, and specifically heart failure.[39, 40] We postulate several possible explanations. The average time from baseline assessment (of biomarker) and diagnosis of heart failure is usually quite long. In PREVEND, this was over seven years.[36] Perhaps the predictive value of biomarkers would increase if measured closer to the clinical stage, when heart failure becomes symptomatic. It also illustrates the diversity and complexity of heart failure. The pathophysiologic pathways induced by hypertension, activation of the adrenergic and renin-angiotensin systems, or inflammation are diverse, though all can potentially lead to left ventricular hypertrophy and HFpEF. Distinguishing between HFrEF and HFpEF based on LVEF is probably not specific enough to distinguish between biologic profiles underlying both syndromes.

Can we still use biomarkers to identify subjects at risk for heart failure? Though the predictive power of all single biomarkers may be moderate, the measurements provide vital clinical information on the pathogenesis of heart failure. We showed that a combined increase in the three strongest biomarkers in PREVEND (NT-proBNP, hs-TnT and urinary albumin excretion) resulted in a seven-fold increased risk for new onset heart failure, compared to subjects with low values of these three biomarkers. Future studies are required to evaluate further options for cardiovascular biomarkers. For instance, different stratification strategies ought to be considered, to improve stratification of subjects at specific risk for heart failure. Additionally, the effect of time to event for every biomarker has not yet been evaluated properly. The effect of sex differences between biomarkers and their associations with outcome should also be accounted for in further studies.

Future perspectives

The primary objective of this thesis was to describe the epidemiology of new onset heart failure, with a special interest for clinical characteristics and biomarkers associated with new onset HFrEF and HFpEF. We expected

our findings could lead to a better algorithm for more accurate identification of subjects at risk for new onset heart failure. In other words, we set out to assess an individual's risk for new onset heart failure based on standard clinical and biochemical variables, similar to the Framingham Risk Score for assessing cardiovascular risk.[41] We have shown that risk parameters with predictive value for new onset heart failure in a community-based cohort can be identified. We have also demonstrated that several specific clinical variables and biomarkers are significantly and specifically associated with either new onset HFrEF or HFpEF. Nonetheless, the actual prediction of heart failure proved fairly inaccurate and remains a considerable challenge, especially for new onset HFpEF. The low discrimination in our risk prediction model for HFpEF (and to a certain extent for HFrEF as well), reflects the diversity and complexity of the heart failure syndrome. Based on our results, we can conclude that a considerable timeframe exists between identification of a certain risk factor and the actual development of heart failure signs and symptoms.

The development of heart failure can be described in two phases. The first phase of heart failure development consists of etiology-specific remodeling, in which compensatory mechanisms preserve the cardiac output, ensuring patients remain asymptomatic. During this period, it is speculated that distinct pathophysiologic pathways underlie the process of left ventricular remodeling and that biomarkers could accurately differentiate between these pathways. At a certain point in time, there is a transition to a decompensated state, with manifest, symptomatic cardiac failure. In this phase, patients are identified by symptoms and hospitalization for decompensated heart failure and biomarkers are have better prognostic value with regard to survival or rehospitalisation. In order to improve therapy, especially for subjects with HFpEF, identification of high-risk subjects in the compensated phase is crucial.

In summary, the present thesis investigated and discussed the epidemiological, clinical and biochemical differences underlying new onset heart failure separately for HFrEF and HFpEF. New pathophysiologic links were identified, providing new insights in the predictive value of clinical characteristics and multiple biomarkers. Additionally, we have confirmed that HFpEF is a complex syndrome, with increasing incidence and high mortality. Early identification of subjects at risk for heart failure, especially HFpEF, remains difficult based on the presently available clinically and biochemically oriented risk prediction model.

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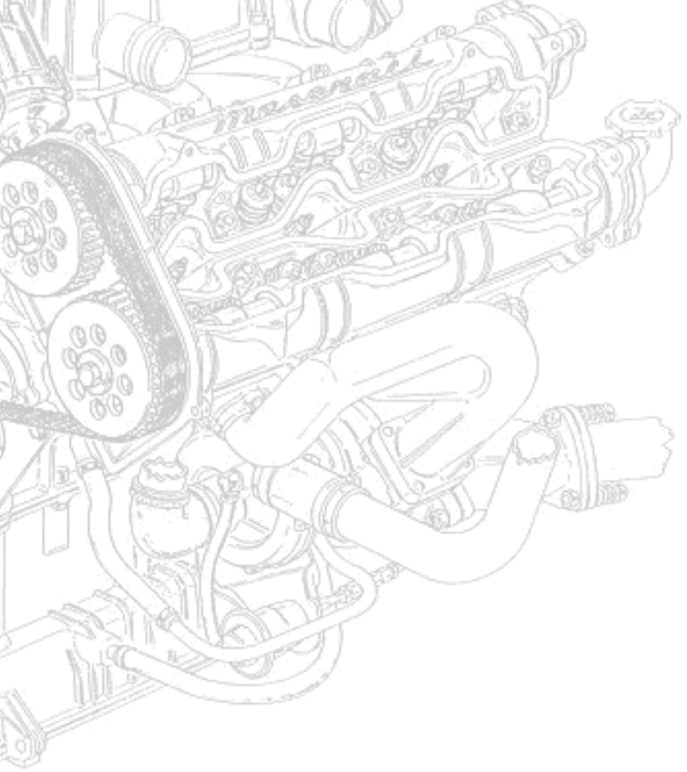


Dutch summary

In dit proefschrift wordt het ontstaan en de manifestatie van hartfalen beschreven, met speciale aandacht voor klinische en pathofysiologische verschillen tussen hartfalen met verminderde ejectiefractie (Engels: HFrEF) en hartfalen met behouden ejectiefractie (Engels: HFpEF).

Het eerste deel van dit proefschrift omvat de epidemiologie van nieuw hartfalen, evenals de klinische karakteristieken en biomarkers voor nieuw HFrEF en HFpEF. In **hoofdstuk 1** en **hoofdstuk 2** wordt een actueel overzicht gegeven over de incidentie en prevalentie van hartfalen. Gedurende de afgelopen tien jaar is er belangrijke epidemiologische informatie gepresenteerd over nieuw ontstaan van hartfalen uit een aantal grote, prospectieve studies met mensen uit een algemene populatie. De huidige beschikbare informatie suggereert dat de incidentie van hartfalen over het geheel aan het dalen is. Dit is het gevolg van succesvolle preventieve aanpak tegen de ontwikkeling van hartfalen. Echter, het moet benadrukt worden dat deze daling vooral komt door de daling van HFrEF patiënten en dat de hoeveelheid patiënten met HFpEF juist toegenomen zou zijn. Dergelijke epidemiologische trends onderstrepen de noodzaak om patiënten met HFpEF te onderscheiden van HFrEF. Eerdere studies suggereerden dat HFrEF en HFpEF misschien wel twee verschillende cardiovasculaire syndromen zouden zijn, en dat beide een verschillende aanpak vereisen. In onze review wordt echter aangetoond dat er momenteel nog zeer weinig cohorten zijn die daadwerkelijk HFrEF van HFpEF kunnen onderscheiden, omdat er geen informatie is over de linker ventrikel ejectiefractie (LVEF). Verschillende risicofactoren voor beide syndromen uit de algemene populatie zijn daardoor nog niet goed gedefinieerd en studies die rechtstreeks onderscheid maken tussen nieuw ontstaan van HFrEF ten opzichte van HFpEF ontbreken. Zodoende wordt in **hoofdstuk 3** de incidentie en epidemiologie van HFrEF en HFpEF beschreven in de Prevention of REnal and Vascular ENdstage Disease (PREVEND) studie uit Nederland. In totaal werden 374 deelnemers gediagnosticeerd met hartfalen, gedurende de 12 jaar waarin ze werden gevolgd. De diagnose HFrEF of HFpEF werd toegewezen door een gespecialiseerde commissie en was gebaseerd op de LVEF en diverse andere parameters, volgens de richtlijnen van de European Society of Cardiology. De waargenomen incidentie van nieuw ontstaan hartfalen in de PREVEND populatie was in overeenstemming met voorgaande epidemiologische studies in algemene populaties. De proportie van patiënten met nieuw HFpEF, vergeleken met nieuw HFrEF, was aanvankelijk relatief laag (34% vs. 66%, respectievelijk),

maar dit trok bij naargelang de studie voortduurde. Dit suggereert hogere incidentie van HFpEF in oudere mensen. Daarnaast werd er duidelijk bewijs geleverd voor een verschillende risicoprofiel voor HFpEF, vergeleken met HFrEF. Het blijkt dat er aanzienlijke klinische verschillen ontstaan, jaren voordat symptomen, als gevolg van hartfalen, duidelijk worden. Afgezien van hogere leeftijd en vrouwelijk geslacht, kwamen een verhoogde urine-uitscheiding van albumine, boezemfibrilleren en nierfunctiestoornissen naar boven als nieuwe risico-indicatoren voor HFpEF. In **hoofdstuk 4** worden deze klinische verschillen tussen HFrEF en HFpEF verder versterkt door het evalueren van de prognostische waarde van meerdere biomarkers voor beide subtypen van hartfalen. Een verhoogd risico op hartfalen werd aangetoond door verschillende biomarkers, en in het bijzonder voor HFrEF. Daarentegen was er geen klinisch relevante associatie van biomarkers met het ontstaan van HFpEF. De toegevoegde waarde per biomarker werd tevens vergroot wanneer algemene bevolking werd gecategoriseerd in laag- en hoog-risico patiënten. Deze eenvoudige stratificatie was gebaseerd op de aanwezigheid of afwezigheid van een cardiovasculaire ziekte bij aanvang van de PREVEND studie. Tenslotte, dit onderzoek omvatte ook de ontwikkeling van een biomarker score, waarbij het risico voor het ontstaan van hartfalen meer dan zevenvoudig toenam, met de combinatie van een verhoogd NT-proBNP, hs-TnT en urine excretie van albumine. In **hoofdstuk 5**, het laatste hoofdstuk uit deel I, is de beste combinatie van standaard klinische en biochemische parameters geëvalueerd, om het eerste voorspellingsmodel voor risico op HFrEF en HFpEF te creëren. Voor dit risicomodel voor hartfalen werden 21 regulier beschikbare variabelen gebruikt en toonde een goede interne validatie en kalibratie. Echter, de voorspellende kracht van het model voor beide hartfalen syndromen was bescheiden en daarom blijft het klinisch nut twijfelachtig. Het voorspellen van risico op HFpEF in het bijzonder, zal een belangrijke uitdaging in dagelijkse klinische praktijk blijven.

In het tweede deel van dit proefschrift worden de eerder genoemde resultaten ondersteund door meerdere onafhankelijke analyses, die de prognostische waarde van alleenstaande biomarkers associëren met slechte cardiovasculaire uitkomst. Urine excretie van albumine in het bijzonder heeft een krachtige prognostische associatie met cardiovasculaire uitkomst, zo blijkt uit gegevens van de verlengde PREVEND Intervention

Trial (PREVEND IT). De PREVEND IT was een gerandomiseerde klinische trial met een 2x2 ontwerp, waarbij patiënten werden gerandomiseerd naar 20mg fosinopril of placebo, en 40mg pravastatine, of met placebo. In **hoofdstuk 6** is de duur van deze studie verlengd tot tien jaar en het was duidelijk dat verhoogde urine excretie van albumine geassocieerd was met een significante toename in cardiovasculaire mortaliteit en morbiditeit, vooral bij patiënten in het hoogste kwintiel van albuminurie (≥50mg/24h). Bovendien, het gunstige effect van fosinopril in het verminderen van het cardiovasculaire risico bleef bestaan na het staken van de behandeling, gedurende verdere 'passieve' follow-up. In **hoofdstuk 8**, een subanalyse van PREVEND IT, werd bij dezelfde deelnemers (≥50mg/24h) aangetoond dat de Framingham Risk Score het tien-jaars risico op cardiovasculaire ziekte aanzienlijk onderschat. Tot slot, in **hoofdstuk 7** worden de resultaten gepresenteerd van de nieuwe biomarker Adrenomedulline. Deze multifunctionele peptide komt voornamelijk tot expressie in endotheelcellen, en is betrokken bij vasorelaxatie, natriurese en het verhogen van het hartminuutvolume. Deze biomarker wordt geassocieerd met ongunstige cardiovasculaire afloop, met name bij personen onder de 70 jaar.

Discussie

Epidemiologie

Hartfalen is een belangrijk probleem voor de volksgezondheid, met een prevalentie van meer dan 6,5 miljoen in Europa en meer dan 26 miljoen wereldwijd. Er wordt geschat dat een op de vijf volwassenen ouder dan 40 jaar hartfalen zal ontwikkelen in hun leven. Als zodanig is hartfalen al herhaaldelijk genoemd als een opkomende epidemie. De toename in de wereldwijde prevalentie van hartfalen in de afgelopen tientallen jaren kan worden toegeschreven aan verschillende factoren: vergrijzing, een toename van de incidentie van cardiovasculaire ziekte, verbeterde behandeling van hartaandoeningen in het algemeen (vooral het acuut coronair syndroom), die alle leiden tot een vermindering van de mortaliteit op korte termijn, en ontwikkeling van hartfalen op langere termijn. Een verhoogd bewustzijn van deze hartfalen epidemie, en het feit dat er meer betrouwbare en gevoelige diagnostische hulpmiddelen beschikbaar zijn (bijvoorbeeld natriuretische peptiden en echocardiografie), zou ook deze relatieve toename van de incidentie en prevalentie van hartfalen kunnen verklaren. Ondanks alles, uit de meest recente studies blijkt de incidentie van hartfalen te stabiliseren, en in sommige groepen patiënten zelfs af te nemen.

De linker ventrikel ejectiefractie (LVEF) classificeert tussen hartfalen met behouden ejectiefractie (Engels: HFpEF) of verminderde ejectiefractie (Engels: HFrEF). Hoewel verschillende afkapwaarden voor de LVEF zijn voorgesteld, is de algemene consensus dat hartfalen met een LVEF boven de 50% wordt beschouwd als behouden. Er wordt geschat dat de LVEF behouden blijft in ongeveer de helft van alle gevallen van hartfalen in de gemeenschap. Epidemiologische gegevens over de incidentie en prevalentie van hartfalen, ingedeeld naar ejectiefractie, en de ontwikkeling ervan in de tijd zijn beperkt. Het beschikbare bewijs suggereert dat de huidige prevalentie van HFpEF toeneemt, in tegenstelling tot HFrEF. Een andere grote studie, die gebruik maakt van gegevens van 275 ziekenhuizen in de Verenigde Staten, bevestigen deze bevindingen. Belangrijker nog, in dit proefschrift stellen we dat deze stijging van HFpEF patiënten zelfs een onderschatting is van de werkelijke HFpEF last. Het niet herkennen van HFpEF in de dagelijkse kliniek kan hierbij een rol spelen, omdat klinische signalen en symptomen van hartfalen de neiging hebben om minder specifiek te zijn, en daarnaast verscheidene comorbiditeiten vaker gelijktijdig voorkomen. Bovendien, studies aangaande de incidentie en prevalentie van hartfalen betroffen patiënten die waren opgenomen in ziekenhuizen, terwijl weinig studies patiënten vanuit de polikliniek gebruikten. Nogmaals, dit geldt met name voor HFpEF, waar een significant deel van stabiele patiënten met benauwdheidsklachten wellicht aan kan lijden.

Onze aandacht is, of zou tenminste moeten verschuiven van HFrEF naar HFpEF. Een belangrijke ontwikkeling, aangezien diverse studies gepubliceerd in de afgelopen jaren hebben aangetoond dat de prognose voor HFpEF even slecht is als voor HFrEF. Aan het begin van de 20e eeuw, de geschatte overleving na de diagnose van hartfalen was 50% en 10%, na 5 en 10 jaar, respectievelijk. Hoewel er het afgelopen decennium verscheidene studies een verbeterde overleving rapporteren, de overleving na hartfalen diagnose blijft nog steeds slecht. Deze trends zijn in overeenstemming met recente grote veranderingen in de behandeling van hartfalen, en suggereren daarmee dat de behandeling van hartfalen effectief is in de algemene populatie. Echter, er moet nog veel vooruitgang geboekt worden. Aangezien de groep HFpEF patiënten toe zal nemen gedurende de tijd, terwijl er nog een specifieke behandeling voor is, zal de prevalentie van HFpEF toenemen. Dit benadrukt de dringende behoefte aan nieuwe therapeutische aanpak van dit syndroom.

Differentiële kenmerken van HFrEF en HFpEF

Er wordt gespeculeerd dat HFrEF en HFpEF verschillende vormen van hartfalen vertegenwoordigen, ofwel bestaan als onderdeel van een hartfalen spectrum. Huidige kennis omtrent structurele, functionele en moleculair biologische processen ondersteunen echter de theorie dat het twee discrete ziekteprocessen zijn. Dit proefschrift levert verder bewijs dat HFrEF en HFpEF verschillende syndromen zijn en dat elk een andere aanpak vereist. De meeste gegevens over HFrEF en HFpEF zijn vooralsnog afkomstig van studies met hartfalen patiënten, waarin retrospectief klinische verschillen tussen patiënten met HFpEF en HFrEF zijn aangetoond. Bij de eerste klinische presentatie, zijn patiënten met HFpEF ouder, vaker vrouw en hebben vaker overgewicht, dan patiënten met HFrEF. Bovendien hebben ze minder vaak onderliggend ischemische hartziekte, terwijl hypertensie en boezemfibrilleren vaker voorkomen. Anderzijds, patiënten met HFrEF hebben vaker een ischemische hartziekte, gedefinieerd als een eerder hartinfarct of ischemische ECG afwijkingen. Andere risicofactoren die zijn geassocieerd met HFrEF zijn diabetes mellitus en een voorgeschiedenis van alcoholmisbruik. Nierfunctiestoornissen zijn een veel voorkomende aandoening in zowel patiënten met HFrEF als HFpEF, het zogenaamde cardiorenaal-syndroom. Onze gegevens suggereren echter dat nierfunctiestoornissen een grotere risicofactor voor het ontstaan van HFpEF zijn, dan voor het ontstaan van HFrEF, gebaseerd op het meten van cystatine C of albuminurie.

We vonden gelijkwaardige resultaten in PREVEND, namelijk evident differentiële klinische kenmerken voor HFrEF en HFpEF. Verschillende clusters van cardiovasculaire risicofactoren kunnen met name worden gebruikt om het individuele risico voor het ontstaan van HFrEF vs. HFpEF in te schatten. Als zodanig kunnen onze bevindingen belangrijke implicaties hebben voor gerichte hartfalen preventiestrategieën. Dit wordt verder versterkt door de waargenomen gemiddelde tijd van start van PREVEND tot de diagnose van hartfalen, welke 7.2 jaar was. Bovendien, gemiddelde tijd tot diagnose van HFpEF (8.3 jaar) was significant hoger dan voor HFrEF (6.6 jaar). Het bestaan van de bovengenoemde verschillende risicoprofielen voor HFrEF en HFpEF, vele jaren voordat de symptomen van hartfalen op de voorgrond komen te staan, weerspiegelt meest waarschijnlijk het lange termijn proces van linker ventrikel remodeling, voorafgaande aan symptomen van hartfalen. Vooral voor asymptomatische

individuen met hypertensie, meer agressieve behandeling met anti-hypertensiva wordt aanbevolen, om verder linker ventrikel remodeling, leidend tot HFpEF, te voorkomen. Vele specifieke risicofactoren voor HFpEF zijn namelijk gerelateerd aan hypertensieve eindorgaanschade, zoals boezemfibrilleren, linker ventrikel hypertrofie en nierfunctiestoornissen - hetzij functionele schade, zoals bij cystatine C of structurele schade, zoals bij albuminurie. Voor HFrEF is een soortgelijke strategie al bewezen effectief gebleken, aangezien therapie gericht tegen linker ventrikel remodeling in mensen na een hartinfarct, aanzienlijk de ontwikkeling van hartfalen vermindert. Terwijl hartfalen epidemiologisch nog steeds beschouwd wordt als een ziekte van de ouderen, begint het proces van de linker ventrikel remodeling al vele jaren eerder. Of vroegere en meer agressieve behandeling van cardiovasculaire risicofactoren voor HFrEF en HFpEF een belangrijke strategie zou kunnen zijn, voor het voorkomen van toekomstig hartfalen blijft onduidelijk.

Biomarkers

De vraag blijft of biomarkers kunnen helpen bij het vroegtijdig identificeren van verhoogd risico op het ontstaan van hartfalen, zoals hierboven beschreven. De aanwezigheid of afwezigheid van biomarkers representeert afzonderlijke pathofysiologische mechanismen, betrokken bij het ontwikkelen van hartfalen en omvat diverse enzymen, biologische stoffen en markers van cardiale myocyten-stress of -letsel. Vele biomarkers zijn momenteel beschikbaar, en geven informatie over verscheidene pathofysiologische processen die de ontwikkeling van hartfalen beïnvloeden. Een aantal biomarkers hebben momenteel een gevestigde plaats in de diagnostiek en behandeling van hartfalen, maar de enige biomarkers die genoemd worden in de meest recente richtlijnen voor hartfalen, zijn NT-proBNP en hs-TnT. De associatie van vele nieuwe opkomende biomarkers met cardiovasculaire ziekte moet nog worden bepaald, zoals bijvoorbeeld bij adrenomedullin, galectin-3, en de neurohormonale biomarkers renine en aldosteron. In dit proefschrift werd de voorspellende waarde van biomarkers voor nieuw ontstaan van hartfalen beschouwd als bescheiden. Met andere woorden, met betrekking tot klinische toepasbaarheid, de toegevoegde waarde per biomarker was laag. Dit is consistent met eerdere studies over de lange-termijns voorspellende waarde van biomarkers voor cardiovasculaire ziekte, en specifiek voor hartfalen. We postuleren enkele mogelijke verklaringen. De gemiddelde tijd van meting van biomarker (start van studie) en de diagnose van hartfalen is over het geheel vrij lang. In PREVEND,

dit was meer dan zeven jaar. Misschien zou de voorspellende waarde van biomarkers toenemen als de bepaling dichter bij het moment zou zitten, als hartfalen symptomatisch wordt. Het illustreert daarnaast ook de diversiteit en complexiteit van hartfalen. De pathofysiologische mechanismen die gang gezet worden door hoge bloeddruk, activering van het adrenerge en renine-angiotensine systeem, of inflammatie zijn divers, terwijl allen kunnen leiden tot linker ventrikel hypertrofie en HFpEF. Onderscheid tussen HFrEF en HFpEF, gebaseerd op LVEF, is waarschijnlijk niet specifiek genoeg om onderscheid te maken tussen de diverse biologische profielen die ten grondslag liggen aan beide syndromen.

Kunnen we nog steeds gebruik maken van biomarkers om mensen met een risico op hartfalen te identificeren? Hoewel de voorspellende kracht voor hartfalen van de meeste biomarkers matig is, de waardes geven belangrijke klinische informatie over de pathogenese van hartfalen. We hebben in dit proefschrift laten zien dat een gecombineerde verhoging van de drie sterkste geassocieerde biomarkers met hartfalen in PREVEND (NT-proBNP , hs-TnT en albuminurie) resulteerde in een zevenvoudig verhoogd risico voor het ontstaan van hartfalen, in vergelijking met deelnemers met lage waardes van deze drie biomarkers. Toekomstige studies zijn nodig om verdere mogelijkheden voor cardiovasculaire biomarkers te evalueren. Bijvoorbeeld, verschillende stratificatie strategieën moeten worden overwogen, om beter hoogrisico patiënten voor hartfalen te identificeren. Bovendien, het effect van tijd van bepaling tot eindpunt voor elke biomarker is nog niet voldoende geëvalueerd. Het effect van geslachtsverschillen tussen biomarkers en hun associaties met uitkomst moet ook worden beoordeeld in verdere studies.

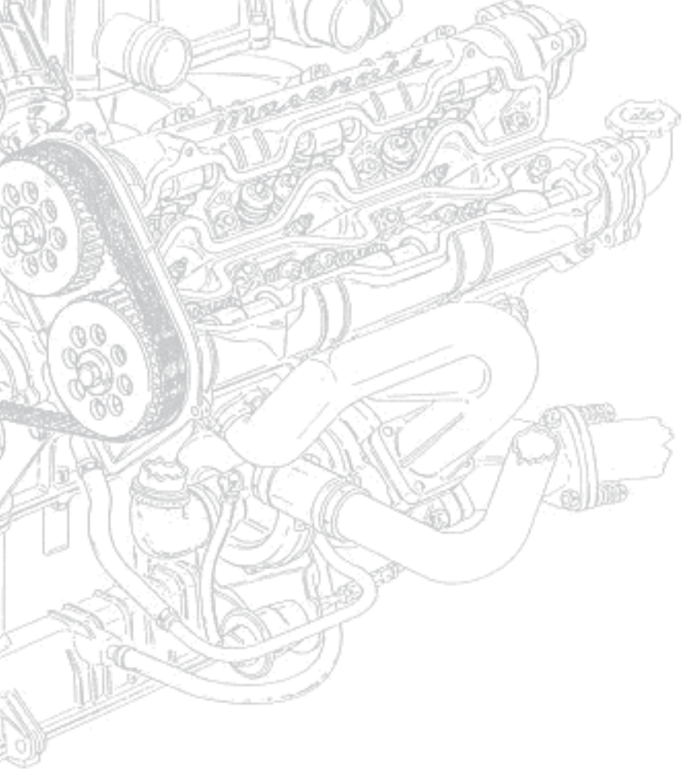
Toekomstperspectief

De primaire doelstelling van dit proefschrift was om de epidemiologie van beginnend hartfalen te beschrijven, met speciale aandacht voor de klinische kenmerken en biomarkers voor het ontstaan van HFrEF en HFpEF . We hadden verwacht dat onze bevindingen zouden kunnen leiden tot een beter algoritme voor meer nauwkeurige identificatie van patiënten met hoog risico op het ontstaan van hartfalen. Met andere woorden, we streefden naar een individuele risico inschatting voor het ontstaan van hartfalen op basis van standaard klinische en biochemische variabelen, vergelijkbaar met de Framingham Risk Score voor de beoordeling van cardiovasculair risico. We hebben risicofactoren aangetoond

met voorspellende waarde voor het ontstaan van hartfalen in een algemene populatie. We hebben ook aangetoond dat een aantal klinische variabelen en biomarkers aanzienlijk en specifiek geassocieerd zijn met ofwel het ontstaan HFrEF of HFpEF. Niettemin, het werkelijke voorspellen van hartfalen bleek vrij onnauwkeurig en blijft nog een grote uitdaging, vooral voor beginnend HFpEF. Het lage onderscheidend vermogen in ons risico voorspellingsmodel voor HFpEF (en tot op zekere hoogte ook voor HFrEF), weerspiegelt de diversiteit en complexiteit van het hartfalen syndroom. Op basis van onze resultaten kunnen we ook concluderen dat er een aanzienlijke tijdspanne bestaat tussen de identificatie van een bepaalde risicofactor en de feitelijke ontwikkeling van hartfalen symptomen.

De ontwikkeling van hartfalen kan worden beschreven in twee fasen. De eerste fase van hartfalen ontwikkeling bestaat uit etiologie-specifieke remodeling, waarin compensatiemechanismen zorgen voor behoud van het hartminuutvolume, en waardoor patiënten klachtenvrij blijven. Er wordt gedacht dat er tijdens deze periode verschillende pathofysiologische mechanismen ten grondslag liggen aan het proces van linker ventrikel remodeling en dat biomarkers nauwkeurig onderscheid kunnen maken tussen deze mechanismen. Op een bepaald punt in de tijd, is er een overgang naar een gedecompenseerde status, met manifest symptomatisch hartfalen. In deze fase worden patiënten klinisch geïdentificeerd door symptomen en ziekenhuisopname voor decompensatio cordis, en biomarkers hebben dan een betere prognostische waarde ten aanzien van overleving of heropname. Om de behandeling en overleving te verbeteren, in het bijzonder voor patiënten met HFpEF, is identificatie van hoogrisico patiënten in de eerste, gecompenseerde fase cruciaal.

Samenvattend, dit proefschrift evalueerde de epidemiologische, klinische en biochemische verschillen die ten grondslag liggen aan het ontstaan van hartfalen, en afzonderlijk voor HFrEF en HFpEF. Nieuwe pathofysiologische mechanismen werden geïdentificeerd, wat nieuwe inzichten geeft in de voorspellende waarde van klinische karakteristieken en biomarkers. Daarnaast wordt andermaal bevestigd dat HFpEF een complex syndroom is, met toenemende incidentie en hoge mortaliteit. Vroege identificatie van patiënten met verhoogd risico op hartfalen, vooral HFpEF, blijft lastig op basis van het thans beschikbare voorspellingsmodel.



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Dr. K. Damman, het laatste lid van de PREVEND hartfalen validatiecommissie. Beste Kevin, dank voor je inzet hiervoor, alsook je bijdrage aan de biomarker paper in dit proefschrift.

Dr. F.W. Asselbergs wil ik graag bedanken voor de introductie in de wetenschap en de vele uren van statistische bijstand toen ik door de bomen het bos nog niet kon zien. Beste Folkert, je hebt mijn enthousiasme voor de wetenschap, maar ook voor de Cardiologie enorm aangewakkerd. De batterij van de laptop staat uiteraard nog steeds op 'hoge prestaties'.

Namens het grote PREVEND team: prof. dr. D. de Zeeuw, prof. dr. R.O.B. Gans, prof. dr. P.E. de Jong en in het bijzonder dr. R.T. Gansevoort en dr. S.J.L. Bakker. Beste Ron en Stephan, jullie zijn voor de meeste van mijn artikelen een vaste waarde gebleken en jullie hebben als 'niet-cardiologen' jullie stempel duidelijk gedrukt op mijn proefschrift. Heel erg bedankt voor jullie tijd en energie.

Alma, Audrey, Brechtel, Carla, Danielle, Marian, jullie zijn een baken van rust (en geduld!) in de hectische wereld van drukke hoogleraren. Het was op z'n minst gezegd een uitdaging om altijd alle afspraken, vakantieaanvragen, declaraties, bijeenkomsten, telefoontjes en korte momenten voor die benodigde handtekening te organiseren. Of gewoon even kletsen, natuurlijk.

Alle werknemers van de TCC voor de technische ondersteuning aangaande alle PREVEND zaken. Jef Everts, dank voor je bijdrage aan de applicatie voor electronische validatie van hartfalen cases. Marco Assman voor alle database en software management. En Paul Koenes, voor alle hulp en geduld als ik voor de zoveelste keer weer iets te vragen of te klagen had over de PREVEND database.

Ontelbare hoeveelheid cola-, bubbels- en taartrondjes (zelden met specifieke aanleiding), de 48-uurs sauna- en jacuzzi-service in de Ardennen, het Oktoberfest, zeilen, paintballen, avonden in het Feithhuis en nachten in de &zo, de afgelopen vier jaren zijn gekleurd door mijn collega's op de LM1. Jullie zorgden voor de goede balans tussen werk en sociaal, en anders was ik de kwaadste niet om deze te verstoren. De leden van de hard-falenkamer (of koffiekamer, sorry Carla), Arjen, Nicolas, Renée, Lennaert, jullie verdienen een speciaal plekje in dit dankwoord. Drie jaar met elkaar in een ruimte zitten kan goed of slecht gaan, maar met jullie was het elke dag goed. Lekkere kopjes koffie van Lennaert (Nicolas… jouw Princess verliest), de raam decoratie van kerst tot voorjaar van Nicolas, de drankkast van Renée (sorry Carla) en de putt-competitie van Arjen, zijn slechts enkele van de vele herinneringen die ik meeneem uit mijn promotietijd. Voor hulp, raad of een biertje waren jullie altijd aanwezig, daarvoor dank ik jullie! Uiteraard noem ik ook You Lan, Ymkje, Wouter, Willem Peter, Vincent, Sven, Suzan, Rosanne, Rob, Pieter Jan, Mattia, Marthe, Marlies, Marjolein, Marieke, Marcelle, Liza, Licette, Karim, Jardi, Ismael, Imke, Ijsbrand, Hessel, Gijs, Ernaldo, Chris, Bart, Ali, en de vele studenten die bij ons zijn geweest, ik hoop dat ik jullie allen nog regelmatig tegenkom, in het Feithhuis of op de 'eerste rij'.

Zonder de Cardio Research geen klinische studies. Van dichtbij heb ik gezien hoe de Research is gegroeid naar goed geöliede machine met haar eigen polikamers en laboratorium. Met name wil ik Geert en Peter bedanken voor de gezellig tijd, de vele momenten kletsen (met of zonder studiemonitor) en jullie enorme inzet voor de Research. Daarnaast natuurlijk aandacht voor Trienke, Saphirah, Margriet, Maaike, Karin, en Jasper, Greetje, Carolien W, Carolien D, Carlien, Bernard, Anke en Anja.

De mix tussen kliniek en Experimentele Cardiologie heb ik altijd als een van de grote pluspunten van mijn promotietijd ervaren. De wetenschappelijke verdieping, van cel tot patiënt, de wekelijkse meetings (met of zonder lunch), en het uitgebreide sociale programma zijn van onschatbare waarde geweest. Wanneer had ik anders nog de kans gekregen om met een geit door de bossen van Drenthe te lopen? Ondanks dat ik nooit een reageerbuis heb aangeraakt en succesvol buiten het laboratorium ben gebleven, veel dank aan Wouter te R, Wouter M, Wardit, Vincent, Silke, Rogier, Reinout (-80 team!), Peter, Michiel, Michael, Megan, Meimei, Martin, Mariusz, Linda, Lili, Leonie, Laura, Jasper, Janny, Irma, Inge, Hong Juan, Hisko, Herman, Hasan, Harmen, Daan, Bo, Bibiche, Beatrijs, Atze, Anne-Margreet, Alexander en alle studenten. Irene (SNIP) en Niek, soms zat ik er bij de GWAS meeting bij alsof ik het niet snapte, en meestal klopte dat ook wel.

Alle PREVEND deelnemers, zonder jullie was dit proefschrift er simpelweg niet geweest.

Mijn paranimfen, Jan Willem Brouwers en Nicolas Schroten. Jan Willem, vanaf het begin merkte ik jouw oprechte interesse in mijn proefschrift. Voor iemand buiten de Geneeskunde is dat al heel bijzonder. Het was voor mij een makkelijke keuze jouw te vragen als paranimf. Je bent veranderd van mijn kleine broertje naar Meester in de rechten en ik ben ontzettend trots op alles wat je al bereikt hebt, je bent een fantastische kerel. Nicolas, mr. Polski (of mr. Proper), partner in crime, ook jouw positie als paranimf lag voor de hand. Met jouw smaak voor wansmaak, gadgets, gastvrijheid in Zwolle / Utrecht, rommel naar elkaar gooien, het was met jou nooit saai. Uiteindelijk zelfs samen ons GVB gehaald. Ik wens je het allerbeste met je opleiding in Amsterdam. Het enige dat nog mist, is een publicatie samen…?

Vrienden en collegae van de ‘eerste rij’, en alle stafleden van ‘de vierde’, de eerste 6 maanden smaken naar meer.

Mijn jaarclub, JC Bravo, ik hoop dat ik jullie weer wat vaker ga zien.

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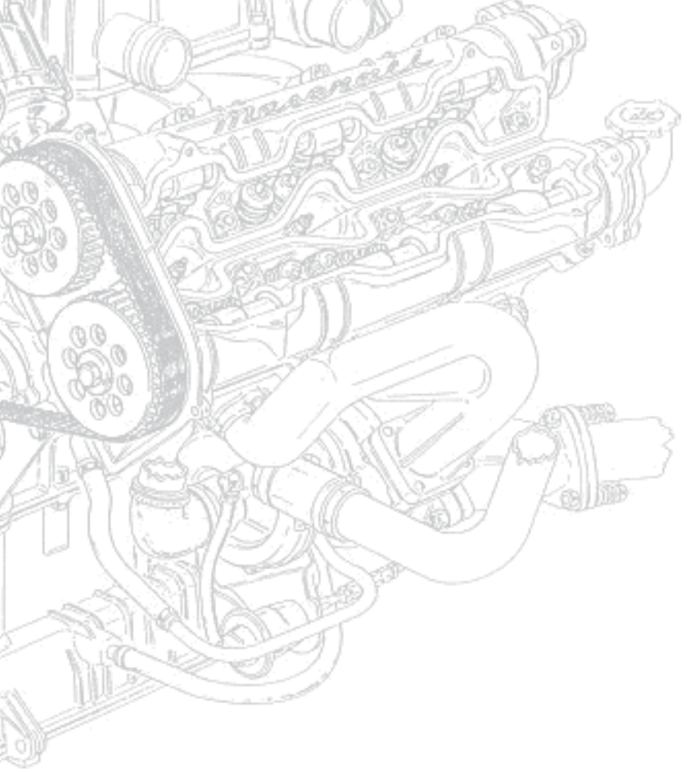
En tot slot, lieve Djai. Het mooiste dat ik heb overgehouden uit mijn promotietijd is niet dit boekje, maar dat ben jij. Met jou is elke dag bijzonder, en ik kijk uit naar ons leven in Groningen!



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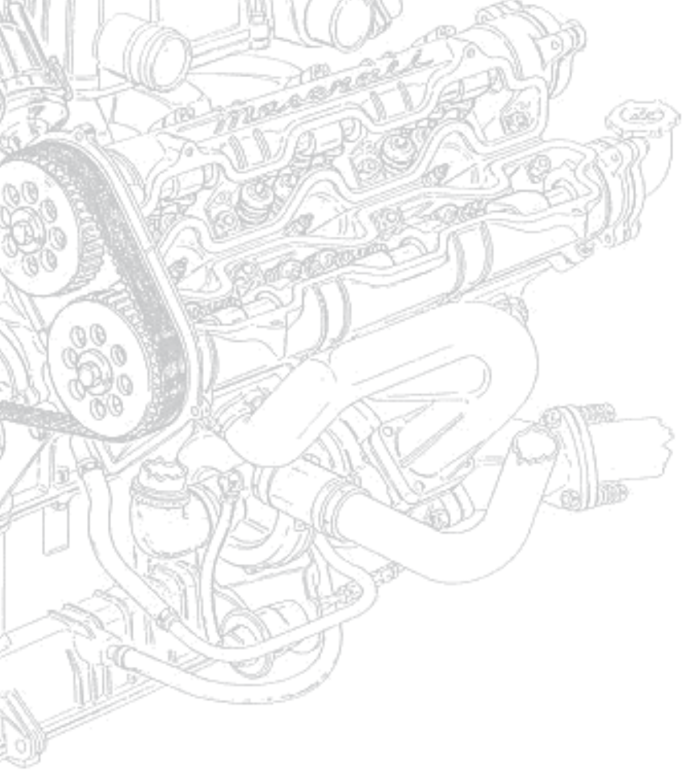
Submitted



Curriculum Vitae

Franciscus Paulus Johannes (Frank) Brouwers werd op 26 mei 1986 geboren in Utrecht en heeft daar gewoond tot hij verhuisde naar Enschede in 1990. In Enschede ging hij naar Openbare Basisschool het Wooldrik, waar hij de 4e groep heeft overgeslagen. In 2003 heeft hij zijn Gymnasium diploma voor zowel Natuur & Techniek als Natuur & Gezondheid behaald aan het het Bonhoeffer College, voorheen het Jacobus College.

Frank ging in 2003 geneeskunde studeren in Groningen. Hij werd lid van studentenvereniging Vindicat atque Polit en heeft naast zijn studie een rijk en actief studentenleven geleid. Hij liep co-assistentschappen in het Universitair Medisch Centrum Groningen, het Delfzicht Ziekenhuis in Delfzijl, het Martini Ziekenhuis Groningen, das Klinikum in Oldenburg, Duitsland, en in het District Hospital in Same, Tanzania. Tijdens zijn co-assistentschappen groeide de interesse in de Cardiologie en begon hij met wetenschappelijk onderzoek onder begeleiding van prof. dr. van Gilst en dr. Asselbergs. Dit resulteerde in een keuze co-assistentschap bij de afdeling Cardiologie en een wetenschappelijke stage bij de Experimentele Cardiologie.

Na zijn afstuderen in november 2009 kreeg dit vervolg in de vorm van een promotietraject bij afdeling Cardiologie van het Universitair Medisch Centrum Groningen onder leiding van prof. dr. van Gilst, prof. dr. van Veldhuisen, prof. dr. de Boer en dr. van der Harst. Tweemaal presenteerde Frank zijn resultaten op het jaarlijks internationaal congres van de *European Society of Cardiology*, waarbij hij eenmaal werd beloond met de Young Investigator Award. Op 27-jarige leeftijd zal Frank dit proefschrift “New onset heart failure: Origin and manifestation” verdedigen. Hij is sinds oktober 2013 begonnen met de opleiding tot cardioloog.